# VASCERN EXCHANGE VISIT ON FRIDAY & SATURDAY JANUARY 20-21, 2023

BELGIUM, ANTWERP

European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

101 Genomes Foundation
Genomics for Rare Diseases

UZA

101 Genomes Foundation

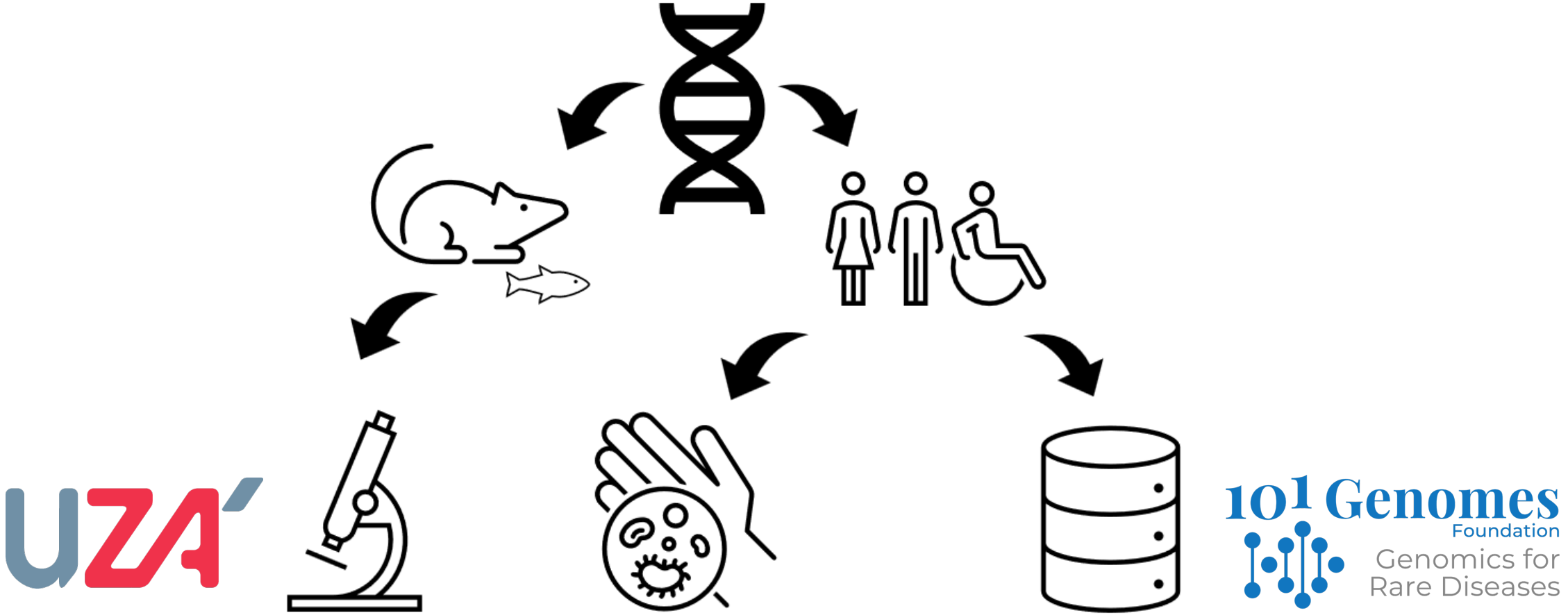
Genomics for Rare Diseases

# VASCERN EXCHANGE VISIT

**UZA – Antwerp, Belgium**

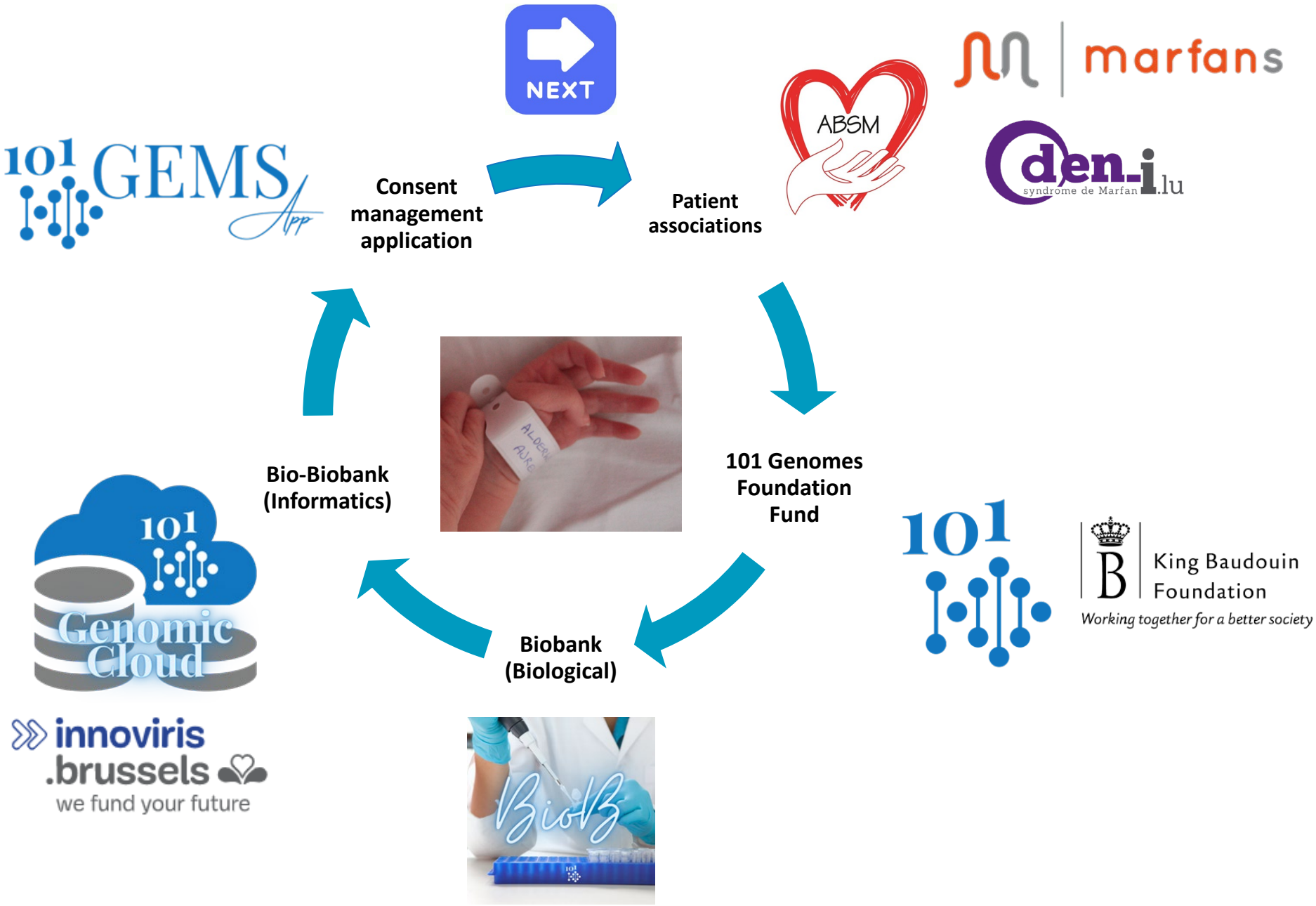
January 20th 2023

# Welcome



**Wet Lab**
Saturday 21/01

**Dry Lab**
Friday 20/01


NEXT
101 GEMS App
Consent management application
ABSM
marfans
den_i.lu
syndrome de Marfan
Patient associations
101 Genomes Foundation Fund
101
King Baudouin Foundation
Working together for a better society
Biobank (Biological)
Bio-Biobank (Informatics)
101 Genomic Cloud
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we fund your future

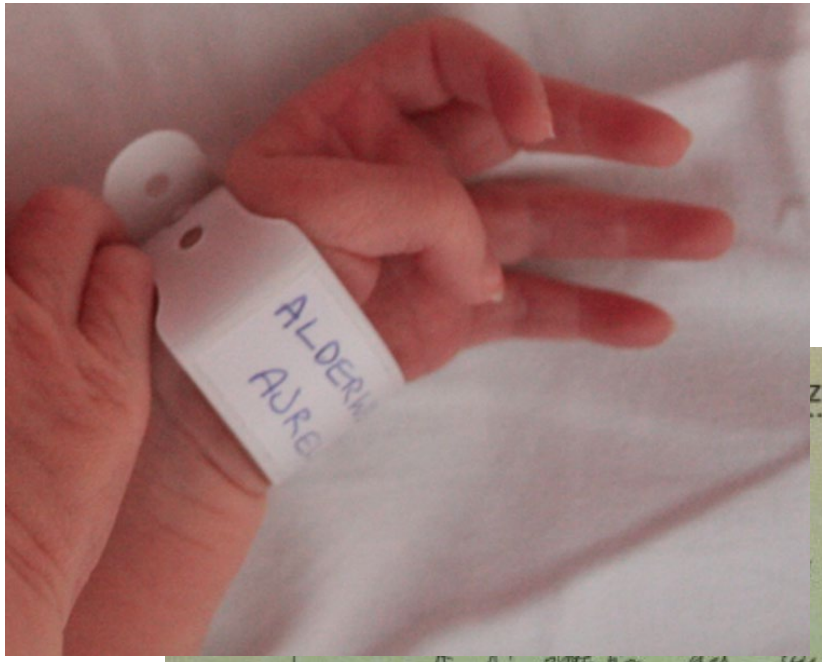
# PART 1
# The 101 Genomes Foundation (F101G)
# Creation, funding and anchorage

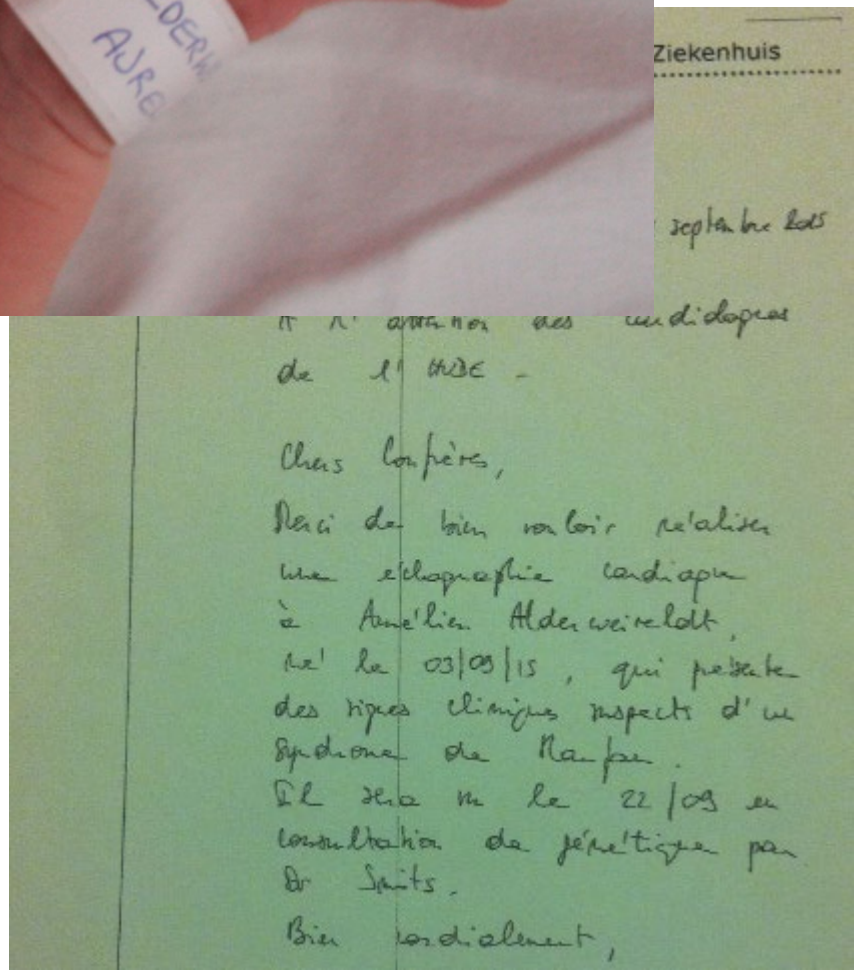
# Creation

# Diagnostic Odyssey

**September 2015**

- Aurélien was born on **September 3rd 2015**.
- Eight days after his birth, on September 11th , the pediatrician who examined him at birth tells us that she suspects a **connective tissue anomaly**.
- She talks about connective tissue abnormalities and **Marfan syndrome** is "evoked" for the first time
- Despite a request from the Brussels geneticist who examined Aurélien, the reference center for Belgium that he contacted refused to carry out a genetic analysis
- A far too long diagnostic odyssey then began





# Diagnostic Odyssey

## Emotional roller coaster

- In the absence of a genetic diagnosis, **various hypotheses were put forward**.
- After a few months, the reference centre agreed to test our child for **Beals syndrome (FBN2)** and this syndrome was ruled out.
- The relief lasted only a few hours: the paediatrician to whom we announced the good news discovered **a heart murmur** in Aurélien.
- Additional examinations carried out within the hour revealed **clear aortic dilatation** accompanied by **regurgitation of the aortic and mitral valves**.
- The reference centre **finally agreed**, 9 months after the first request, to test Aurélien for Marfan syndrome.
- After many months without treatment and a worrying lack of weight gain, Aurélien **finally received appropriate drug treatment**.

Review | Open Access | Published: 01 June 2006

**Congenital contractural arachnodactyly (Beals syndrome)**

Ergül Tunçbilek & Yasemin Alanay

*Orphanet Journal of Rare Diseases* **1**, Article number: 20 (2006) | Cite this article

**21k** Accesses | **38** Citations | **4** Altmetric | Metrics

**Abstract**

Congenital contractural arachnodactyly (Beals syndrome) is an autosomal dominantly inherited connective tissue disorder characterized by multiple flexion contractures, arachnodactyly, severe kyphoscoliosis, abnormal pinnae and muscular hypoplasia. It is caused by a mutation in *FBN2* gene on chromosome 5q23. Although the clinical features can be similar to Marfan syndrome (MFS), multiple joint contractures (especially elbow, knee and finger joints), and crumpled ears in the absence of significant aortic root dilatation are characteristic of Beals syndrome and rarely found in Marfan syndrome. The incidence of CCA is unknown and its prevalence is difficult to estimate considering the overlap in phenotype with MFS; the number of patients reported has increased following the identification of *FBN2* mutation. Molecular prenatal diagnosis is possible. Ultrasound imaging may be used to demonstrate joint contractures and hypokinesia in suspected cases. Management of children with CCA is symptomatic. Spontaneous improvement in camptodactyly and contractures is observed but residual camptodactyly always remains. Early intervention for scoliosis can prevent morbidity later in life. Cardiac evaluation and ophthalmologic evaluations are recommended.

*Waiting for the results is particularly difficult to manage, but we make a wonderful encounter...*

# Diagnostic Odyssey

**August 2016**

- **The diagnostic odyssey** ended 11 months later with the discovery of a ***de novo*** **mutation on exon 26 of our child's FBN1 gene**.
- This discovery confirmed that, as a result of a **spontaneous mutation**, Aurélien is suffering from a **rare disease called Marfan Syndrome**.
- Aurélien was diagnosed during his first year of life, and it is explained to us that he falls into the category of people with a "neonatal" or " early onset" form of Marfan syndrome.

# Diagnostic Odyssey

***The anguish of not knowing***

*"Le plus dur, c'est de ne pas savoir. Une fois qu'on a identifié la maladie, on peut établir un plan d'action"*
Ludivine Verboogen, maman d'Aurélien, 2 ans et demi

Partager sur Facebook

## Vivre avec une maladie rare

*À l'âge de dix mois, le diagnostic génétique est tombé : Aurélien e*
*Marfan, une maladie rare qui touche les tissus conjonctifs. Une fo*
*se sont plongés dans l'étude de cette maladie et même de la géné*
*Fonds 101 Génomes, co-géré par la Fondation Roi Baudouin et la*
*veut mettre à la disposition des scientifiques un outil bioinformati*
*re*

D
A
a
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F
d
a
perturbe la production de fibrilline, une protéine essentielle au bo
conjonctif. Or ce tissu est un peu la glue qui tient ensemble tout
affecté, il en résulte diverses conséquences qui touchent l'ensem
principalement chez les Marfans d'atteintes cardiovasculaires, o
squelettiques", explique Ludivine Verboogen.

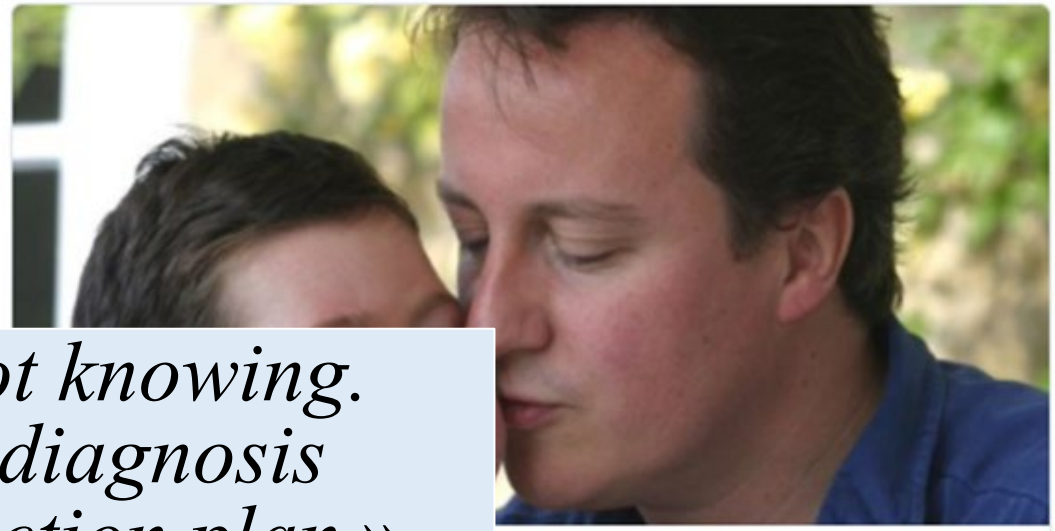
**Plan d'action**
Le diagnostic a été un choc, mais aussi un soulagement, poursuit-elle : "Le plus dur, c'est de ne pas savoir. Une fois qu'on a identifié la maladie, on peut établir un plan d'action. Cela a quelque chose de rassurant."

Fondation 101 Genomes a retweeté

**David Cameron** @David_Cameron · 28 févr.

On world @rarediseaseday, what I learnt from our son's rare disease & how genetic testing, like that carried out by @illumina, is making a transformational change in healthcare, ending the anguish & uncertainty #ShowYourRare

À l'origine en anglais



**disease**

Originally published in The Times on 28 February 2018. (Photo credit: Roger Taylor/ Rex Features) Picture this. The most precious thing in the world

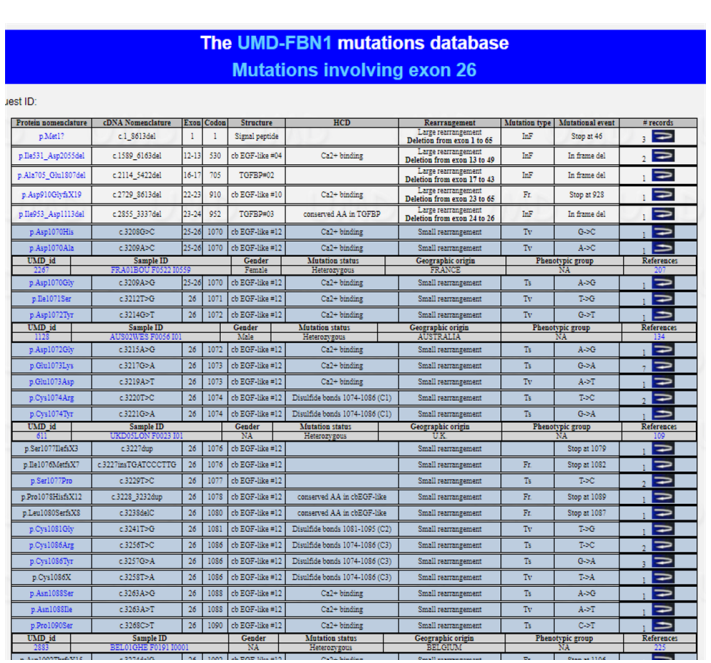
linkedin.com

*« The hardest is not knowing. Once you have a diagnosis you can create an action plan »*

# Diagnostic Odyssey

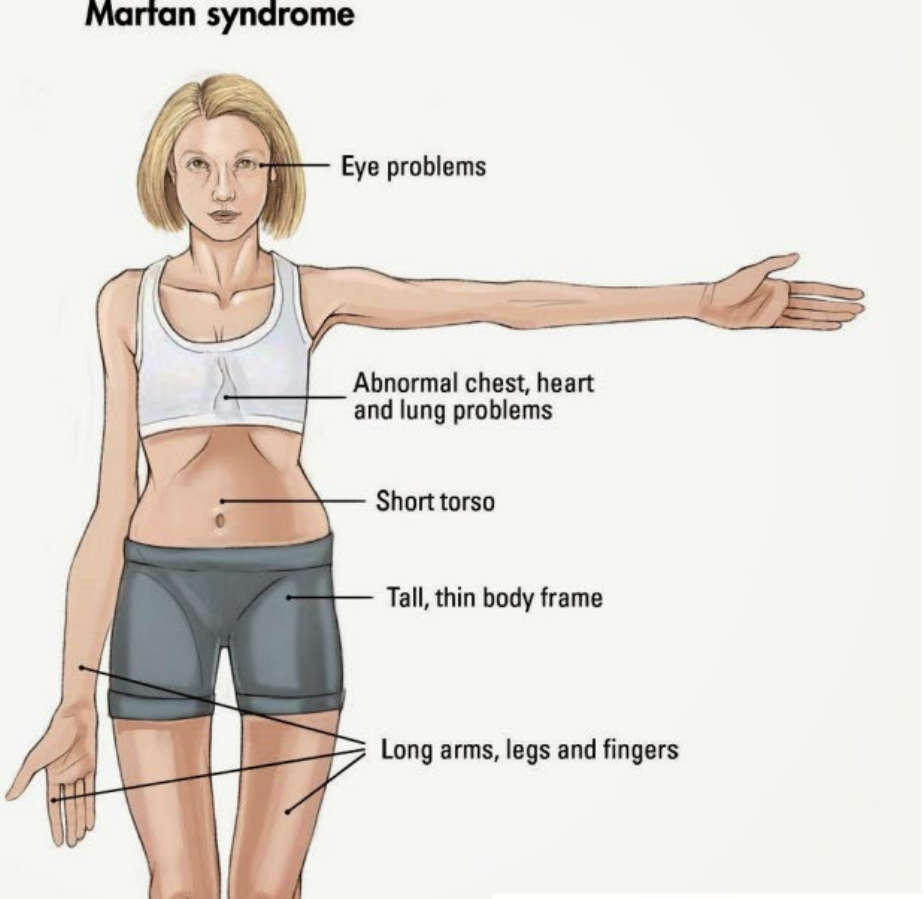
## UMD-FBN1

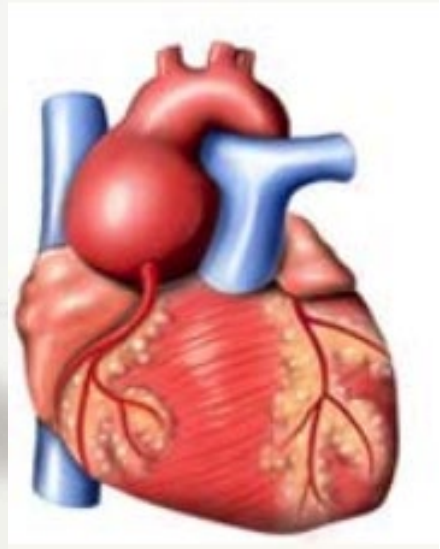
- On the way back from the hospital, Romain **“googled”** Aurélien’s pathogenic mutation that we just received and discovered the UMD-FBN1 database
- This database is available for free at [www.umd.be/FBN1/](www.umd.be/FBN1/)
- It was largely funded by the **French association of patients with Marfan Syndrome**.
- It inventories **3044 mutations of the FBN1** gene identified as being at the origin of Marfan syndrome.
- **UMD-FBN1 feeds the work of many researchers and is an important tool for the diagnosis of the disease**.
- **It appeared** on UMD-FBN1 that the mutation harbored by my son **had already been observed in another patient**. This was the beginning of a new questioning.




marfans

# Marfan syndrome (MFS)
# & neonatal Marfan Syndrome (nMFS)



# Marfan

## FBN1 & fibrilline

- Marfan syndrome results from an **anomaly in the connective tissues** that hold the cells that make up the human body together.
- This abnormality is caused by a **defect in the fibrillin protein** encoded by the **FBN1 gene** following a pathogenic mutation.
- **The disease is multisystemic** and affects, among other things, the **musculoskeletal, pulmonary, ocular and cardiovascular systems**.
- The main danger for patients with the syndrome is that of **aortic dissection**, the consequences of which are generally fatal.

# Marfan

**The intensity of the afflictions is very variable (even within families)**

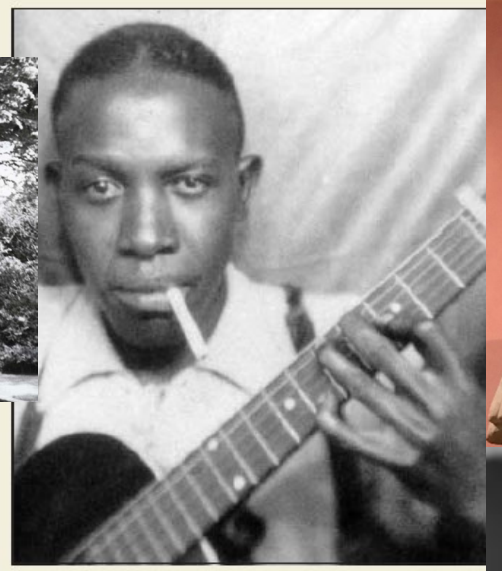

Javier Botet

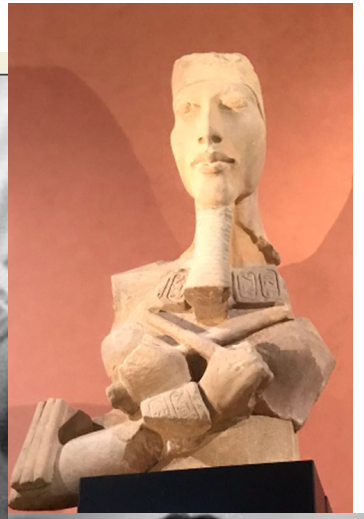
- Some people affected by the syndrome have few disorders.
- While others are severely affected, sometimes severely handicapped and their life expectancy can be quite reduced.
- Between these two extremities, we find the majority of Marfan patients who are sometimes severely handicapped by the disease and who must regularly control the dilation of their aorta.

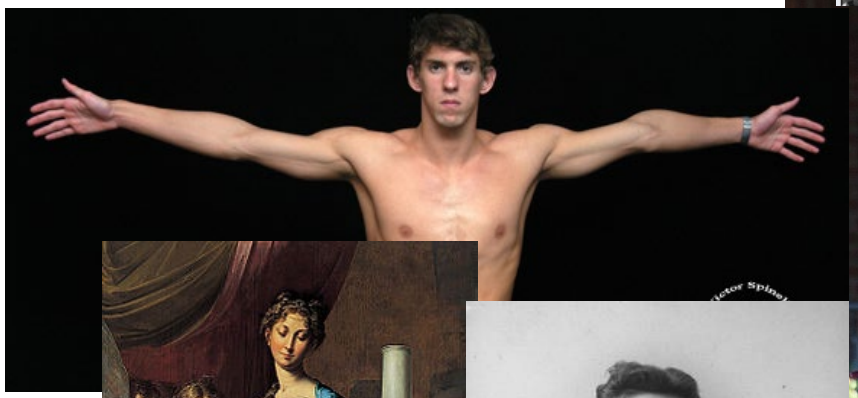
**In the current state of scientific knowledge, the cause of this great variability in the extent and intensity of the damage is not yet well understood.**

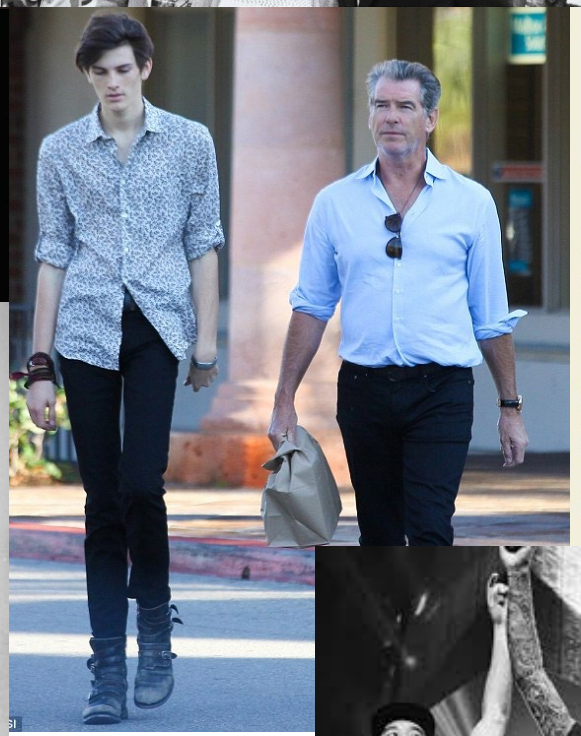
# Marfan

**Never heard of them and suddenly they are everywhere!**





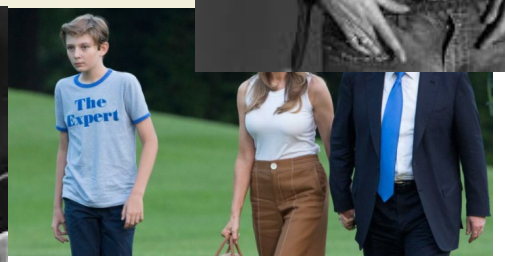




So what does looking back teach us? Now comi
up to 20 years in general practice, I can reflect that
in my personal experience I have seen Marfan's
syndrome on four occasions, most recently, sadly, i
retrospect, after the sudden premature death of on
of our young patients.

And then it dawned on me; that in my 20 years
practice, to my knowledge I have seen only one
death due to aortic dissection—on a cold dark wint
night many years ago, "on her hands and knees
howling like a dog."

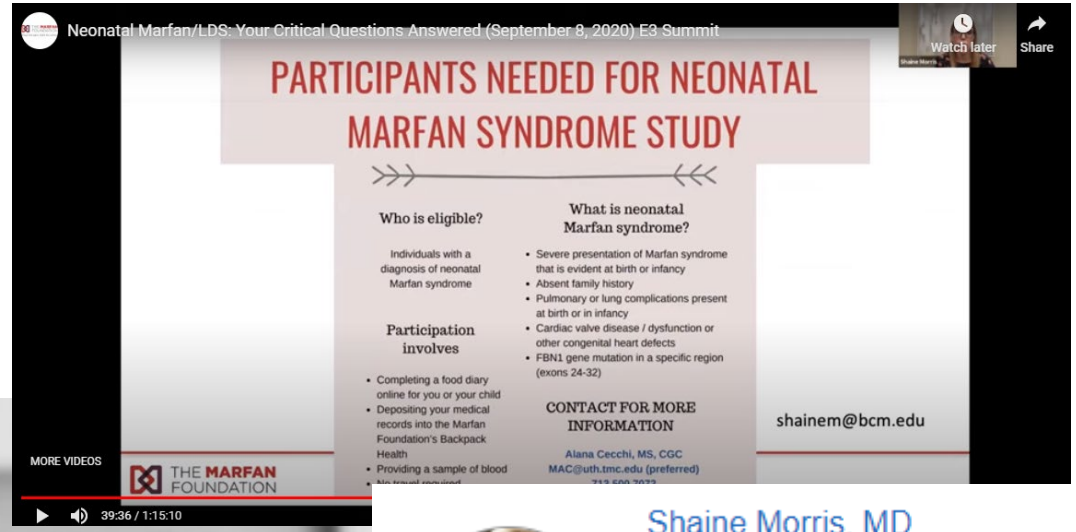
David Connell *GP principal, Fyvie Oldmeldrum Medical Group, Inverurie (dg.connell@virgin.net)*



# Neonatal Marfan

**A very different story**

**https://www.facebook.com/groups/800864546956681**




Shaine Morris, MD

Associate Professor of Pediatrics - Cardiology

Texas Children's Hospital

Send message | View bio




Published in final edited form as:
*Cell*. 2016 April 21; 165(3): 566–579. doi:10.1016/j.cell.2016.02.063.

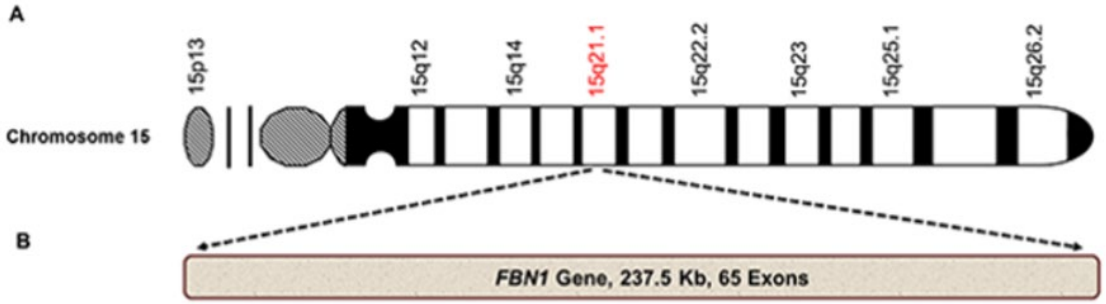
**Asprosin, a Fasting-Induced Glucogenic Protein Hormone**

Chase Romere[1], Clemens Duerrschmid[1], Juan Bournat[1], Petra Constable[1], Mahim Jain[2], Fan Xia[2], Pradip K. Saha[1], Maria Del Solar[8], Bokai Zhu[1], Brian York[1], Poonam Sarkar[3], David A. Rendon[3], M. Waleed Gaber[3], Scott A. LeMaire[4], Joseph S. Coselli[4], Dianna M. Milewicz[5], V. Reid Sutton[2], Nancy F. Butte[3], David D. Moore[1], and Atul R. Chopra[1,2,*]

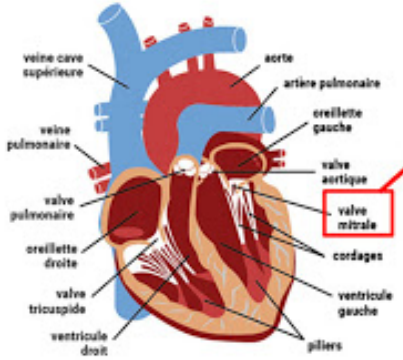
[1]Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030, USA

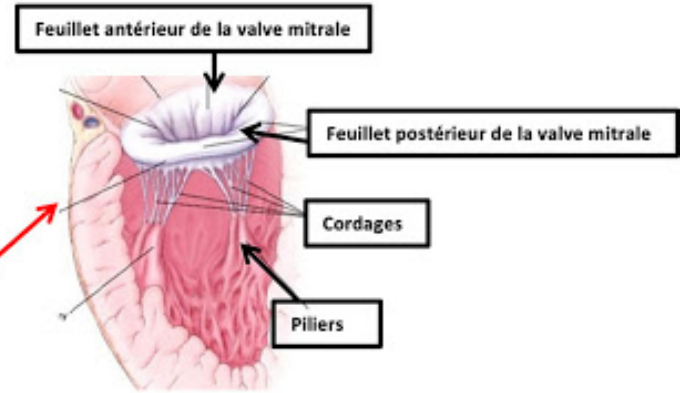
# Neonatal Marfan

**Exons 24-32 et mitral valve**




- These are almost always spontaneous cases: **de novo**
- Genetic analysis reports that these cases are usually (but not always) found when a pathogenic mutation occurs in the core of the FBN1 gene on **the interval of exons 24 to 32**
- A signature of this form is the rapid affection of the **mitral valve**




**What is "Neonatal" Marfan syndrome**

- Also called "Infantile", "Severe", or "Early-onset"
- Features:
  - Downward slanting and deep-set eyes
  - Aged-looking face
  - Crumpled ears
  - Loose skin
  - Early onset of skeletal features
    - Pectus
    - Scoliosis
    - Contractures/joint laxity

# Neonatal Marfan

## Statistical life expectancy

- Some authors report that the **statistical life expectancy** for this particular form is as low as **16.3 months:**

  « *Marfan syndrome (MFS) (OMIM 154700) is an autosomal dominant disorder of fibrous connective tissue involving the ocular, skeletal, and cardiovascular systems. MFS patients present with clinical variability, in which the rare neonatal Marfan syndrome (nMFS) has the most severe presentation in early childhood. The prognosis of nMFS is very poor,* ***with a mean survival age of only 16.3 months****. Valvular insufficiencies and diaphragmatic hernias have been associated with shorter survival in patients diagnosed before the age of 1 year. […] The term neonatal Marfan syndrome was first used in 1991 to describe the most severe phenotype of MFS similar to cases previously known as infantile Marfan syndrome, congenital Marfan syndrome, and severe perinatal Marfan syndrome. Recently, it has been suggested that the term neonatal MFS should be replaced by early onset and rapidly progressive MFS to represent the most severe features of MFS in early childhood* »

  PENG Q. et al., « *A novel fibrillin-1 gene missense mutation associated with neonatal Marfan syndrome : a case report and review of the mutation spectrum* », BMC Pediatrics, 30 avril 2016, 16:60, DOI 10.1186/s12887-016-0598-6

# Genomics

# Genomics

**Prof. Guillaume Smits (IB)² | HUDERF – ERASME**

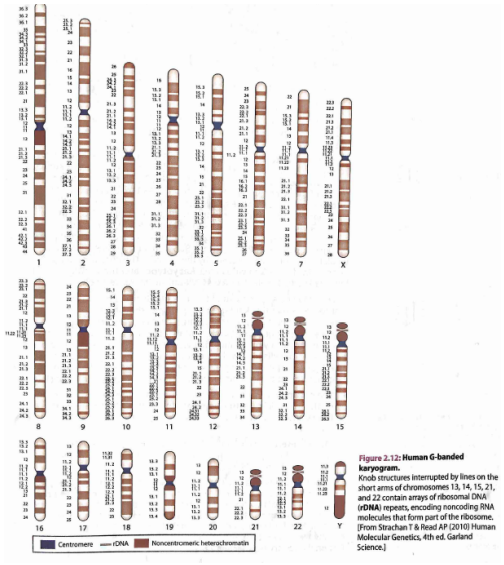
- After the shock of the nMFS diagnosis, **we returned to the geneticist** who follows Aurélien since his second week of life: Prof Guillaume Smits.
- He **patiently answered** our **very many** questions.
- With his explanations, **we progressively understood** that we could, perhaps, **try to help our son and other children living with rare diseases**.

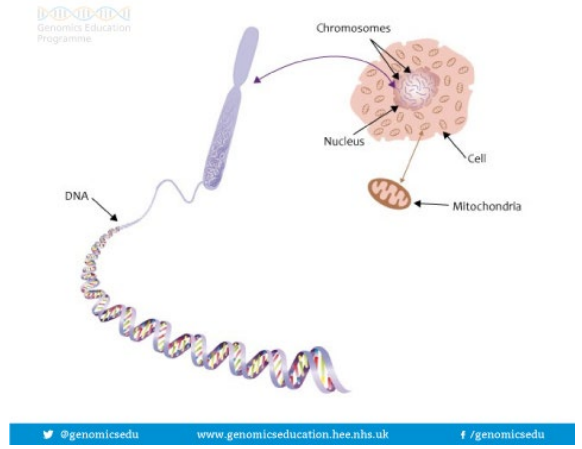
# 20,000 genes

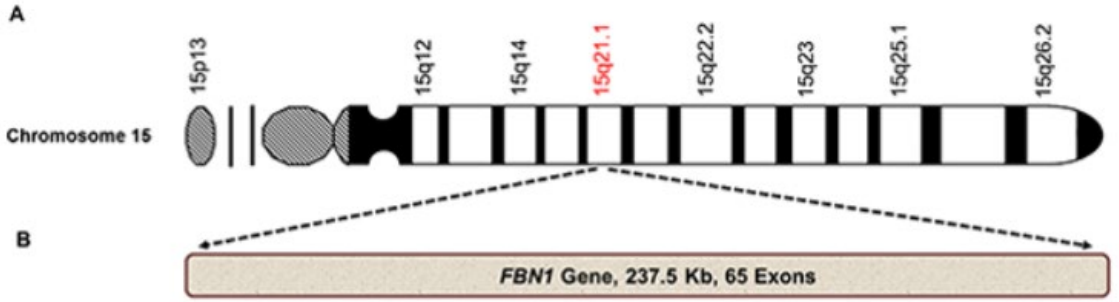
## 23 pairs of chromosomes

- Our cells keep **23 pairs of chromosomes** in their nucleus which are unique to us.
- Chromosomes contain a large proportion of the **20,000 genes (DNA)** that store the information needed to produce the proteins that determine our **phenotype** (set of observable traits).
- **Chromosome 15** contains the **FBN1 gene** which allows the production of **fibrillin** which is deficient (or insufficient in Marfans).

*Note: in addition to the DNA contained in the chromosomes, there is also mitochondrial DNA (stored outside the cell nucleus).*



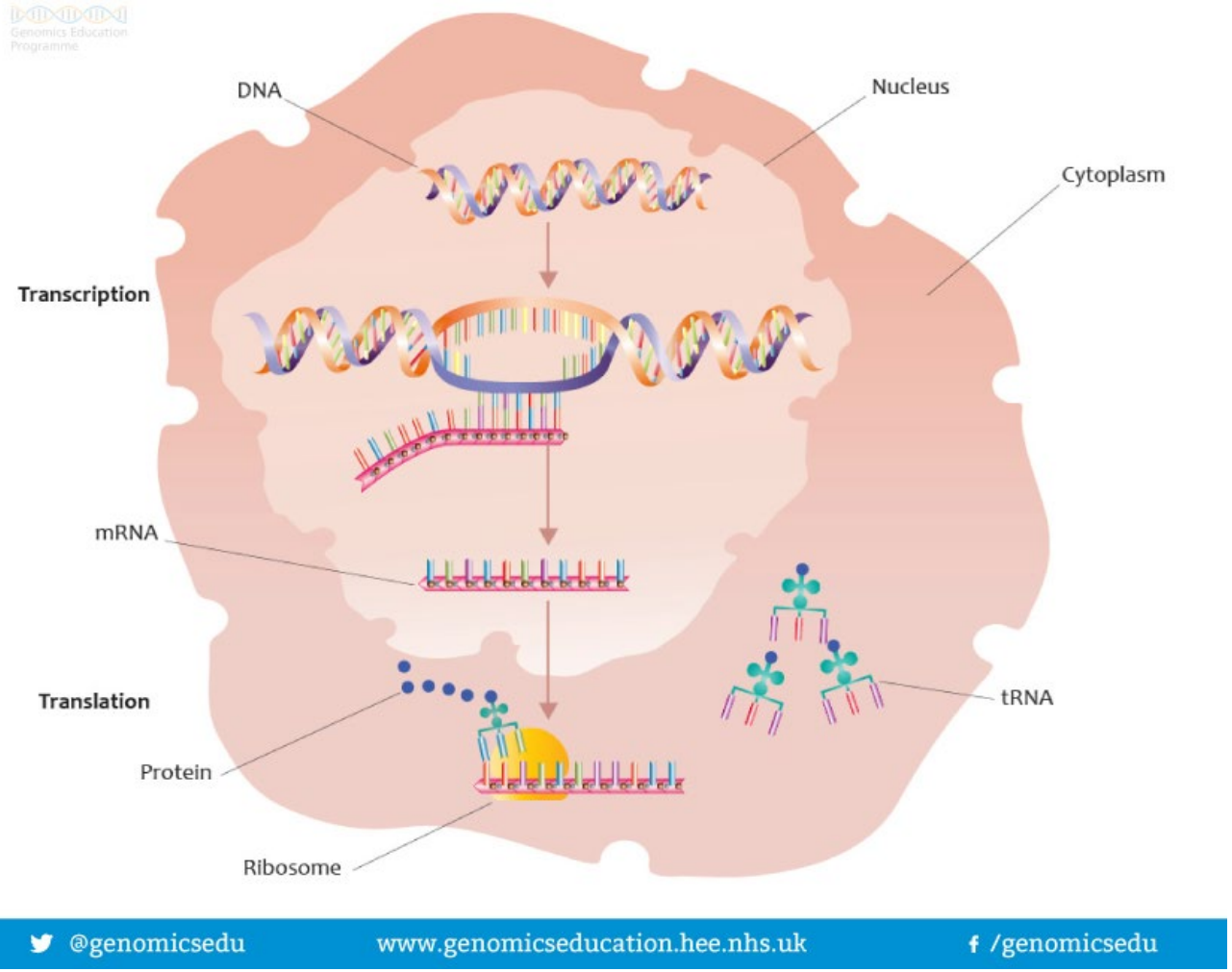



# DNA & RNA

## Genome and Exome

- There is an intermediate stage in which the genes (**DNA**) generate copies of their coding sequences (**RNA)** which enable the synthesis of proteins outside the cell nucleus.
- The **genome** is all the genetic information (coding or not, chromosomal or mitochondrial) of a human being (3 billion nucleic bases).
- The **coding exome** is the set of regions of the human genome that are directly involved in the production of proteins **(3% of the genome)**.



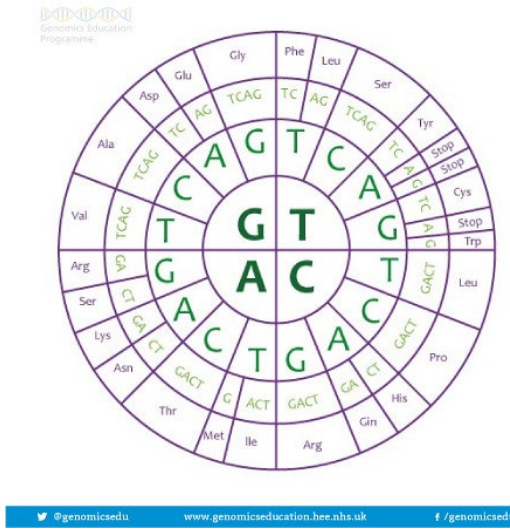
# Nucleotides

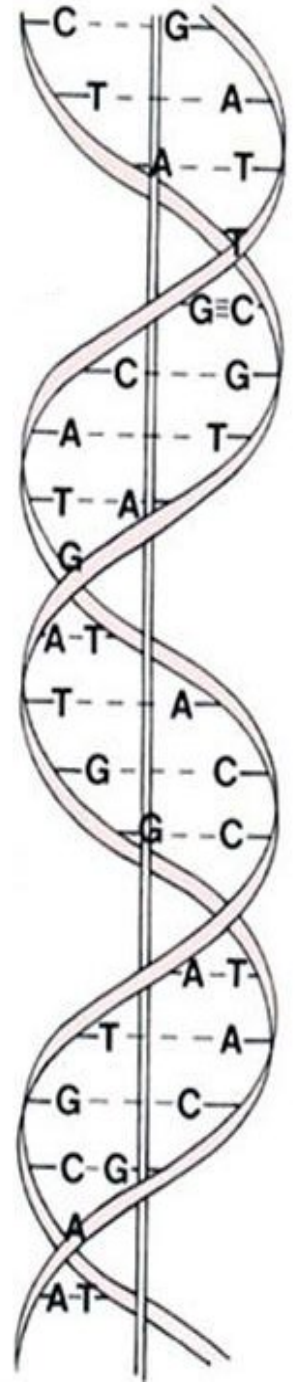
**The alphabet of the genome**

- Our genes are "written" with nucleotides: **A**, **C**, **T** and **G**
- For **adenine**, **cytosine**, **thyline** and **guanine**.
- Nucleotides are **the letters of the alphabet** with which our genome is written.
- The "book" of the **human genome** has **3 billion letters**, an alignment, **a sequence**, of 3 billion A, C, T, G nucleotides.

**This sequence of 3 billion letters is 99,9% identical for all human beings.**

Adenine
Cytosine
Thymine
Guanine



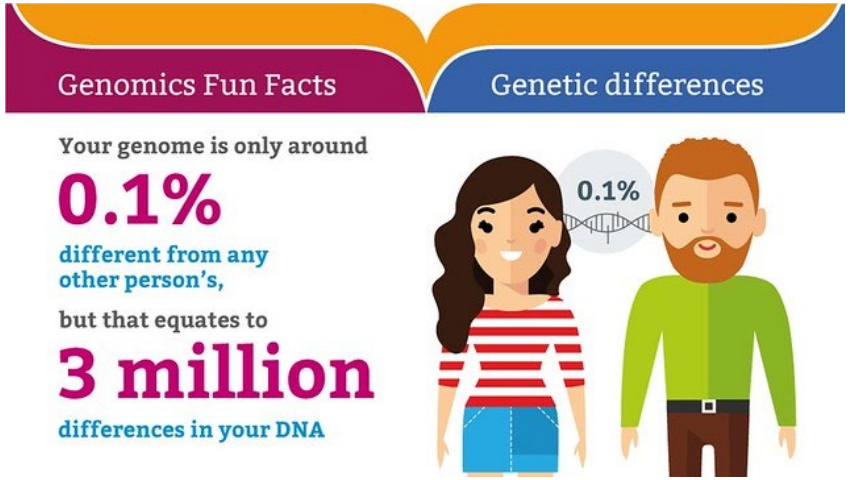



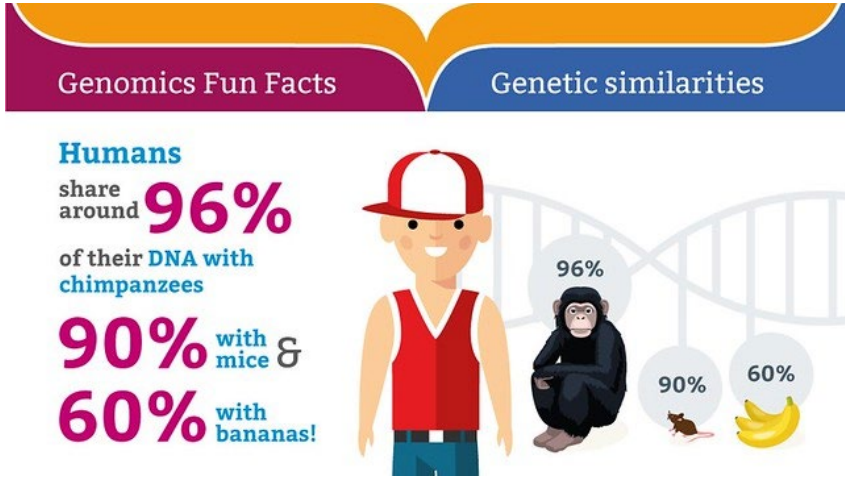
# 99,9% + 0,1%

**Humanity, the human being...**

- This percentage of 99,9% forces us to question notions such as the **brotherhood** of **mankind** since « **our genome** » is 99,9% common with the rest of humanity
- This 0,1% variation represents a difference of about **3 million nucleotides** in 'our' genomes
- These 3 million differences are **scattered throughout the genome**, making them **extremely difficult to identify**.
- Most of these variations do not have **a directly identifiable impact on the** health of individuals.

**We carry millions of mutations that do not affect our health.**



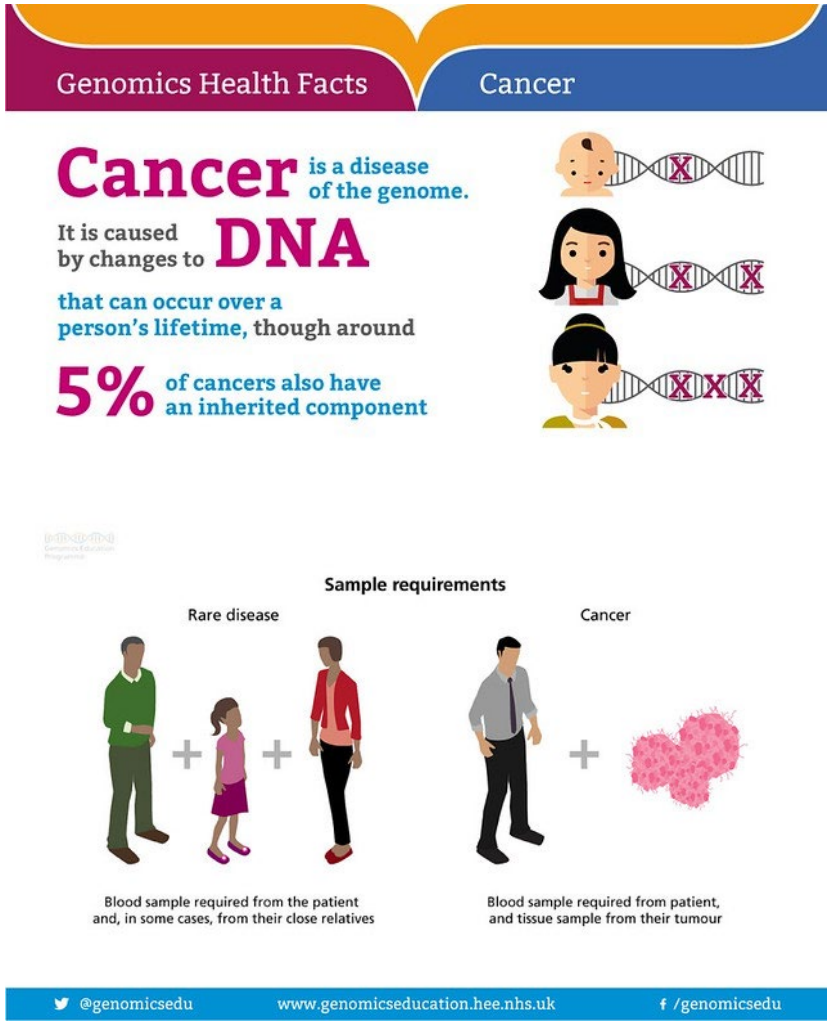



# Diseases

**Diagnosis and therapy**

- Most of these variations do not have **a directly identifiable impact on the** health of individuals.
- However, in certain circumstances, it is **crucial to** identify specific individual variations of 0,1% as this opens the way to the **diagnosis** of certain **diseases** (rare or not) and helps to understand the development of certain **cancers**.

**WHY?**



# Classification of variants (1/2)

**Interpretation of variants is difficult**


DNA HAS ALL YOU CAN ASK FOR .
DNA HAS ALL YOO CAN ASK FOR .

DNA HAS ALL YOU .
DNA HAS ALY OUC ANA SKF OR

DNA HAS ALL LOU CAN ASK FOR .

Courtesy of Prof. Guillaume Smits

# Classification of variants (2/2)

**Benign, pathogenic and VUS**

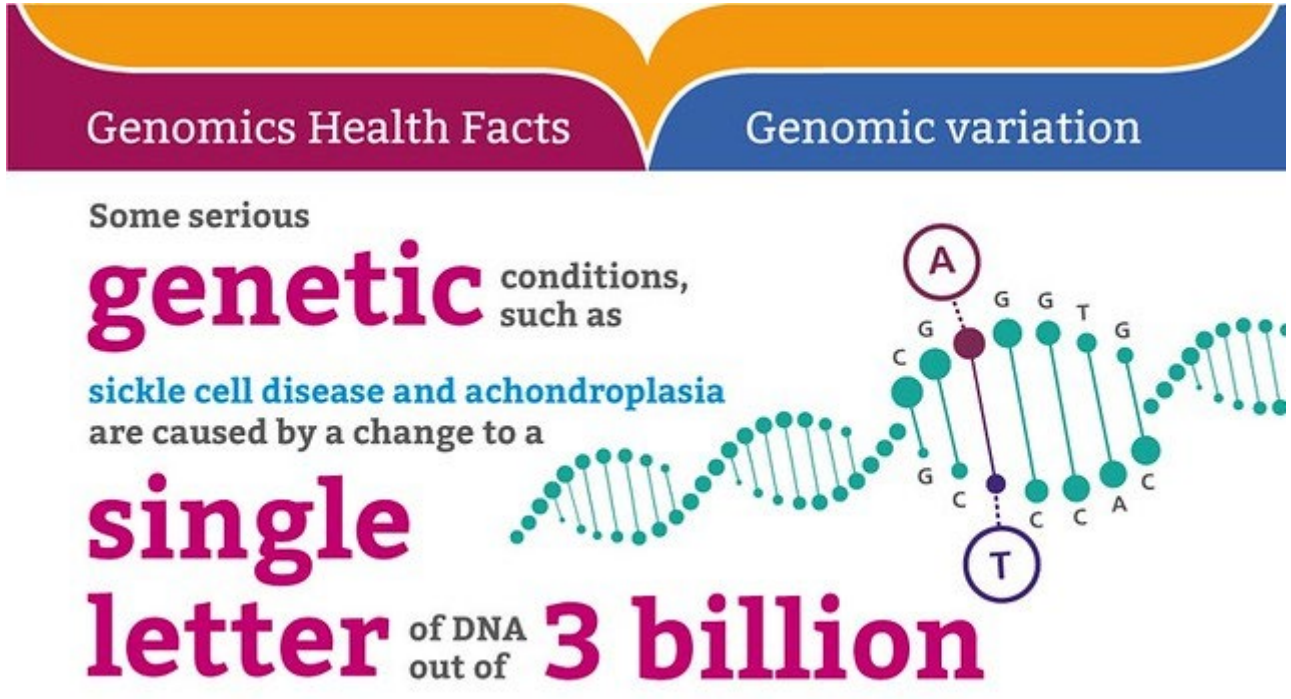

Courtesy of Prof. Guillaume Smits

# Mutations that do not affect us

## MyFBN1

# Single-gene disease

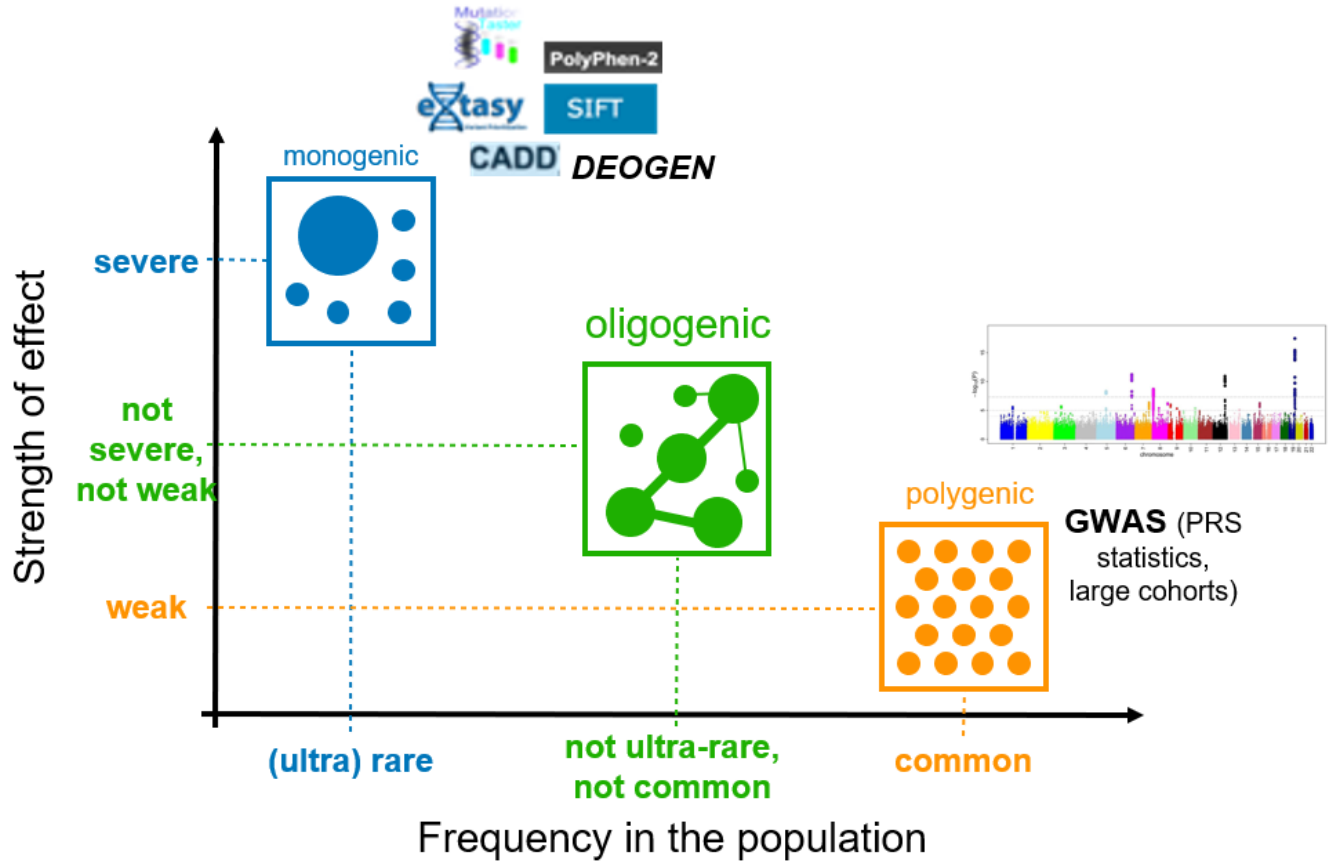
**One in three billion nucleotides changed and nothing will ever be the same again...**




https://www.genomicseducation.hee.nhs.uk/image-library/

# Mono, oligo & polygenic diseases

## Gene network

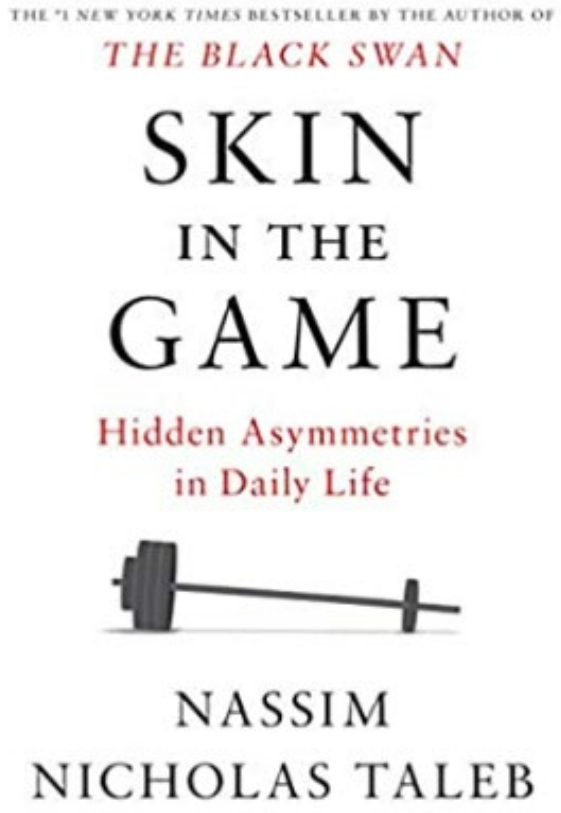



McCarthy, M. I., Abecasis, G. R., Cardon, L. R., Goldstein, D. B., Little, J., Ioannidis, J. P., & Hirschhorn, J. N. (2008). Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nature reviews genetics*, *9*(5), 356.

Courtesy of Professor Tom Lenaerts MLG-IB2-ULB

# Mono, oligo & polygenic diseases

## Genes network




*Understanding how the subparts of the brain (say, neurons) work will never allow us to understand how the brain works.*

A group of neurons or genes, like a group of people, differs from the individual components—because the interactions are not necessarily linear. So far we have no f***ing idea how the brain of the worm *C. elegans* works, which has around three hundred neurons. *C. elegans* was the first living unit to have its genes sequenced. Now consider that the human brain has about one hundred billion neurons, and that going from 300 to 301 neurons, because of the curse of dimensionality, may double the complexity. So the use of *never* here is appropriate. And if you also want to understand why, in spite of the trumpeted "advances" in sequencing the DNA, we are largely unable to get information except in small isolated pockets for some diseases, same story. Monogenic diseases, those for which a single gene plays a role, are quite tractable, but anything entailing higher dimensionality falls apart.

**Nassim Taleb**, Skin in the Game 'Hidden Asymmetries in Daily Life', Chapter 2. The Most Intolerant Wins: The Dominance of the Stubborn Minority, Appendix to Book 3, 2017

# Genomic revolution

# Genomics

## A technological revolution


Today the emergence of new generation sequencers has paved the way to three different approaches to the study of genes:

1. The **"traditional" sequencing** of **individual genes (or by panels of a few genes);**
2. New generation sequencing (NGS) of the whole exome called **Whole Exome Sequencing (WES) 3% of the genome** and;
3. New Generation Sequencing (NGS) of **the entire genome** called **Whole Genome Sequencing (WGS)**.

**With the new sequencers, scientists have gradually entered the era of genomics**

| Genomics | vs | Genetics |
|---|---|---|
| • The study of an organism's complete set of genetic information.<br>• 'Genome'- the complete genetic information of an organism.<br>• The genome includes both genes and non-coding DNA. | | • The study of heredity<br>• The study of the function and composition of single genes.<br>• 'Gene'- specific sequence of DNA which codes for a functional molecule. |

**Human sample (blood, saliva, hair, etc.)**

*Short read: Illumina*
*Long read: PacBio*

**Volume = +/-200 Gigabytes per WGS in 30x (=coverage)**

**FASTQ**

"*In the area of DNA sequencing, the FASTQ file format has emerged as another de facto common format for data exchange between tools. It provides a simple extension to the FASTA format: the ability to store a numeric quality score associated with each nucleotide in a sequence*"

COCK, P. et al. "*The Sanger FASTQ file format for sequences with quality scores, and the Solexa/Illumina FASTQ variants*", Nucleic Acids Research, 2010 (published online 16 December 2009), Vol. 38, No. 6 1767–1771 doi:10.1093/nar/gkp1137

**BAM**

BAM is a compressed version of the FASTQ

"*The Variant Call Format (VCF) Version 4.2 Specication*", 8 Mar 2019, https://samtools.github.io/hts-specs/VCFv4.2.pdf

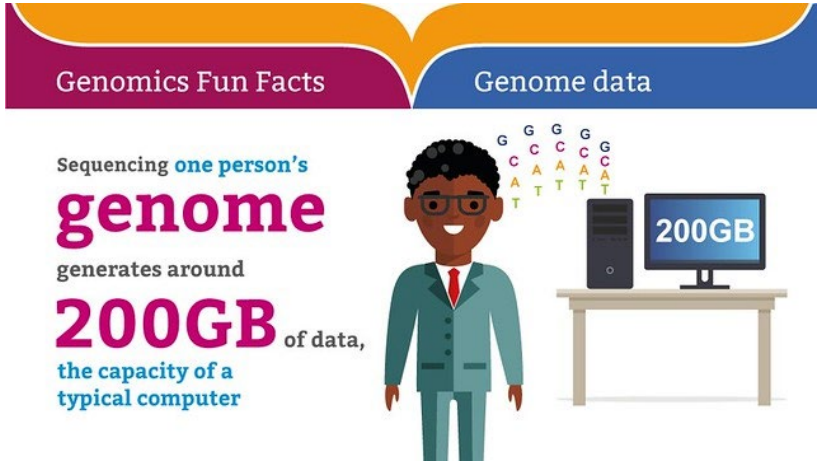
**VCF Variant Call Format**

"*VCF is a text file format (most likely stored in a compressed manner). It contains meta-information lines, a header line, and then data lines each containing information about a position in the genome. The format also has the ability to contain genotype information on samples for each position*".

"*The Variant Call Format (VCF) Version 4.2 Specication*", 8 Mar 2019, https://samtools.github.io/hts-specs/VCFv4.2.pdf

# What?

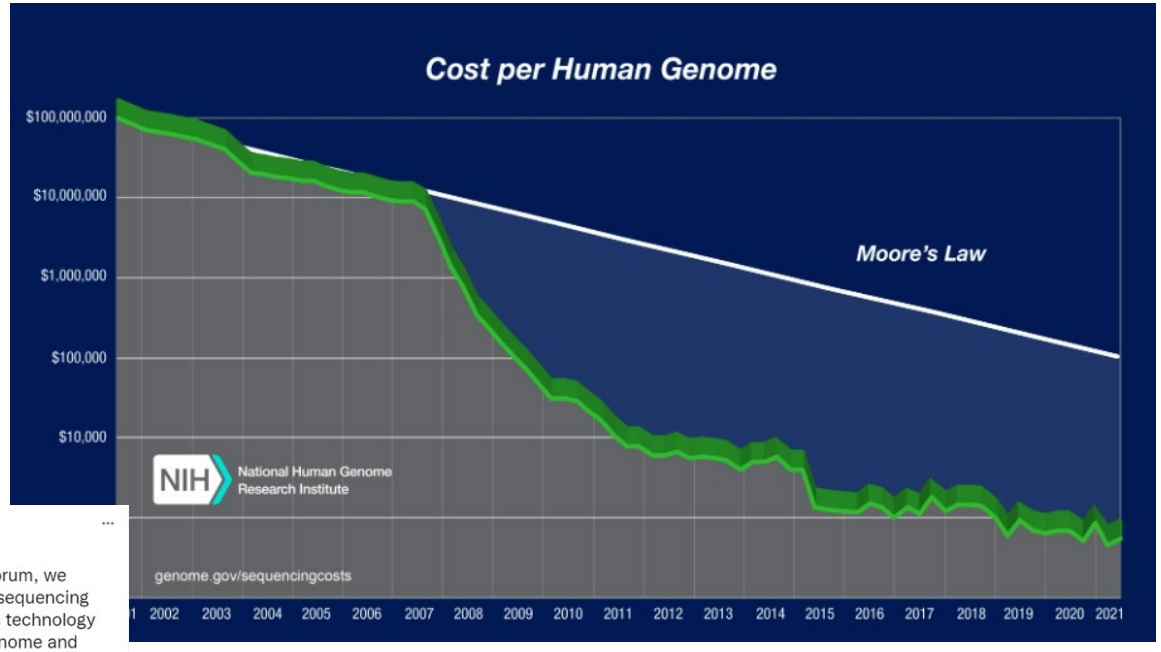
## High level description of the functioning of a new generation sequencer (NGS)



# Prices are going down

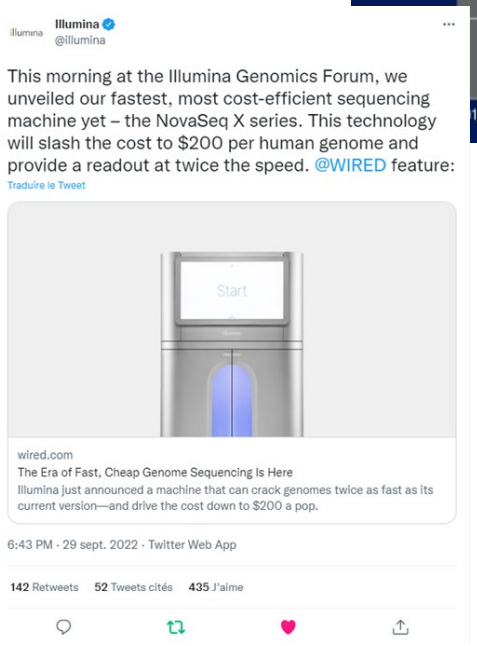
**Less than $1000 for a WGS**

DNA Sequencing Costs: Data (genome.gov)




And the gradual decrease in sequencing costs is helping this transition:

- The cost of sequencing has risen from **$100,000,000** per genome **in 2001** to
- **$1,000** per genome **in 2018.**
- **$800** per genome **in 2021**.
- **$200** per genome in **September 2022?**



# The world may not be ready…

## … for a WGS 30x at $100

"*"My hope is that with the $100 genome we'll start to see some breakthrough studies that will help us better understand how genomics translates to disease and health," deSouza said.*

*The $100 price is still has challenges to overcome, the CEO said.*

*"**Two things** need to happen for us to get to that price point. One is we need to do **engineering work**," he said. "The second one, which is equally important, **is to make sure that our customers have been thinking about what they could do if they had a hundred-dollar genome**."*

BROWN K., "*A $100 Genome Within Reach, Illumina CEO Asks If World Is Ready*", Bloomberg, **27 February 2019**.
https://www.bloomberg.com/news/articles/2019-02-27/a-100-genome-within-reach-illumina-ceo-asks-if-world-is-ready

# Short-read vs Long-read

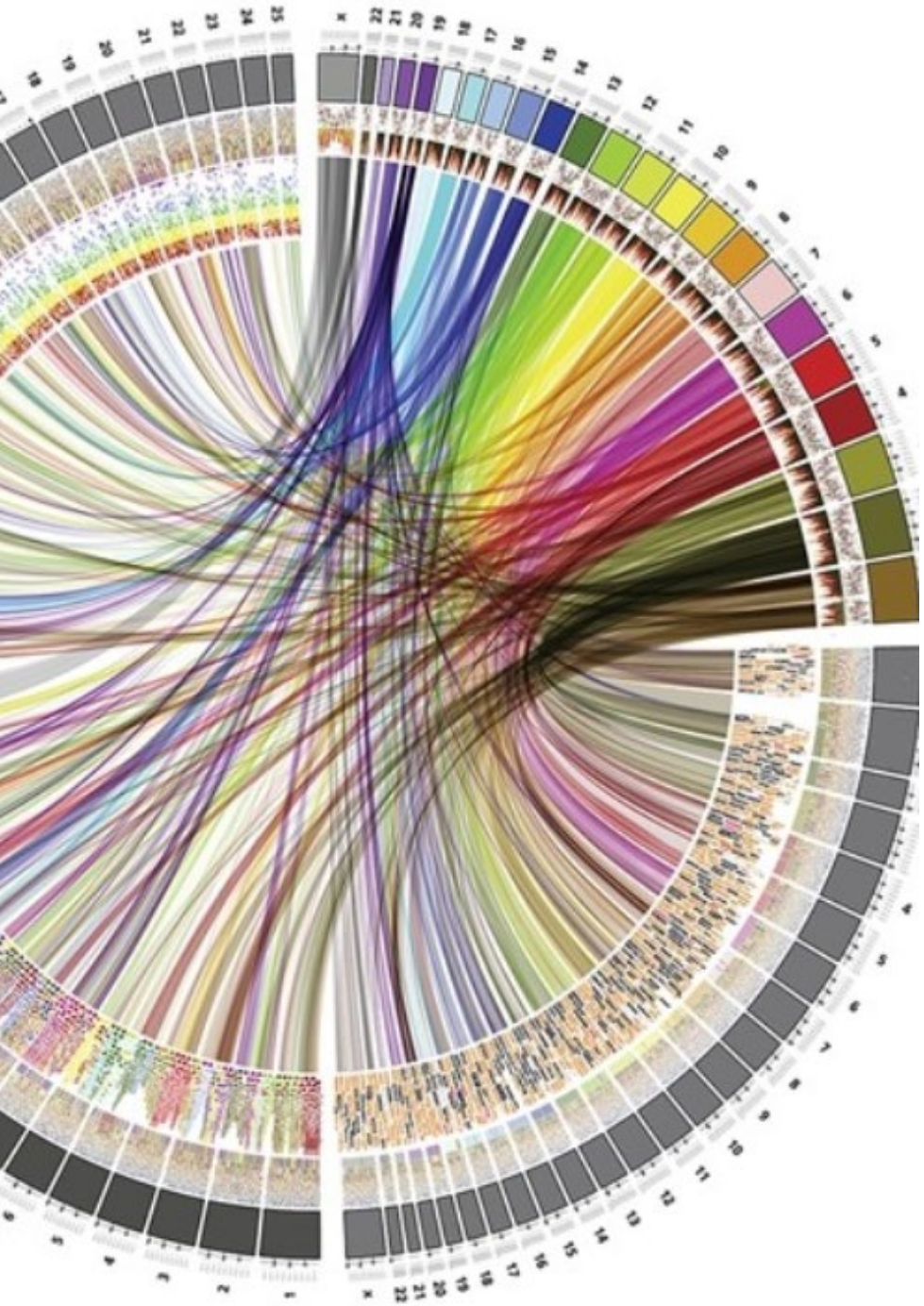
**Rising competition**

## Oxford Nanopore, the disruptive unicorn gunning for Illumina

Elizabeth Cairns

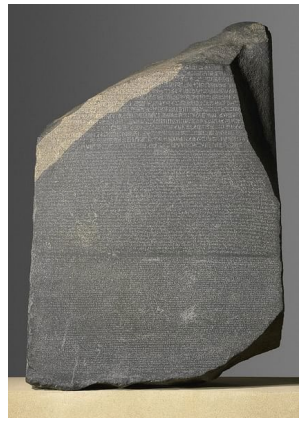
Can the company's $1.5bn valuation be justified when last year it took just $23.5m in orders?

[Oxford Nanopore, the disruptive unicorn gunning for Illumina | Evaluate]



# Rosetta Stone

## Mapping the galaxy of the genome



- The addition of each new sequenced genome progressively **improves** the understanding of the **“human genome”**.
- Each new sequenced genome - shared and coupled with phenotypic data - contributes to “**mapping the genome”** and to **understanding the interactions between different genes.**
- Genome knowledge opens the way to **personalized medicine**.
- **And this is essential in the field of rare diseases**

# Protective Genes

# The Resilience Project

**Reanalysis**

nature biotechnology

ARTICLES

Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

CHEN R. et al., « *Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases* », Nature Biotechnology, 34, 531–538 (2016) doi:10.1038/nbt.3514, Received 29 July 2015 Accepted 12 February 2016 Published online 11 April 2016. Disponible à l'adresse: https://www.nature.com/nbt/journal/v34/n5/pdf/nbt.3514.pdf

- In this project, **589,306 "genomes"** (actually a combination of WES and WGS) collected **at random** in other contexts **have been re-examined.**
- This study identified **13 apparently healthy adults** who carry pathogenic mutations that should have caused severe rare diseases in them that normally develop in childhood.

- The people discovered by the **Resilience Project should have been sick but are not**.
- These people may be protected by the **action of protective modifier genes**.

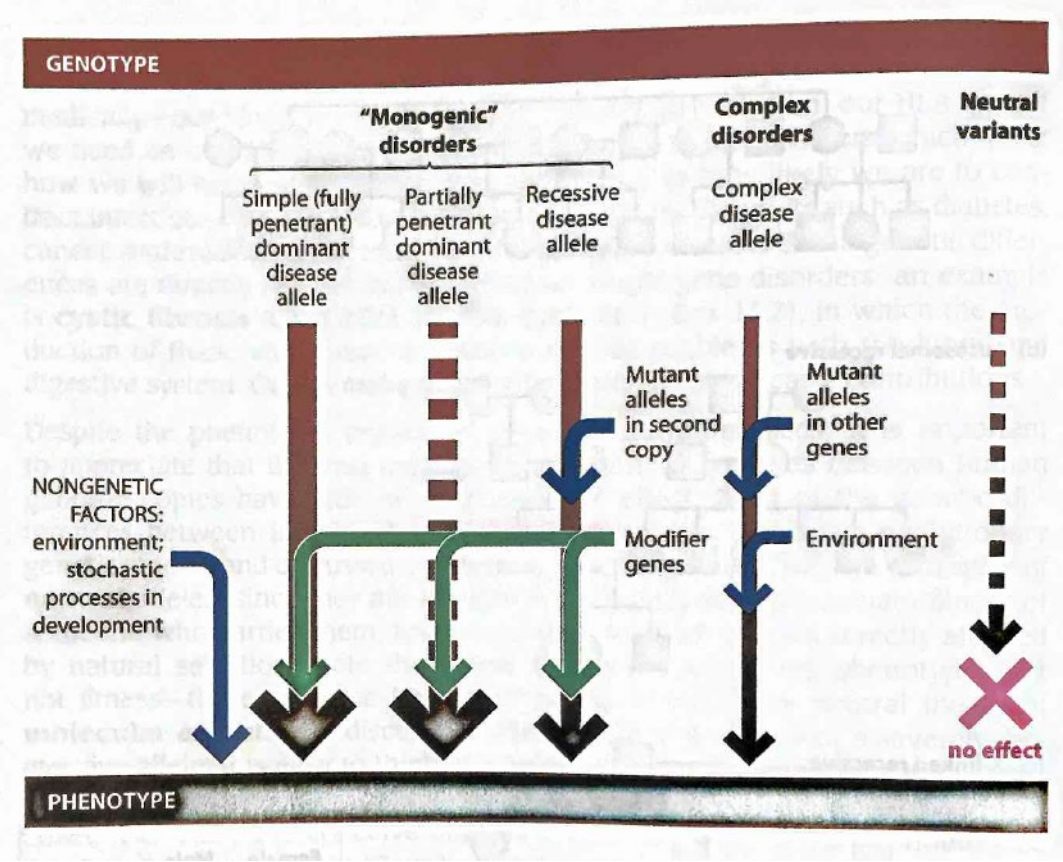
gnomAD

genome aggregation database

# Protective Genes

## Modifier & protective gene

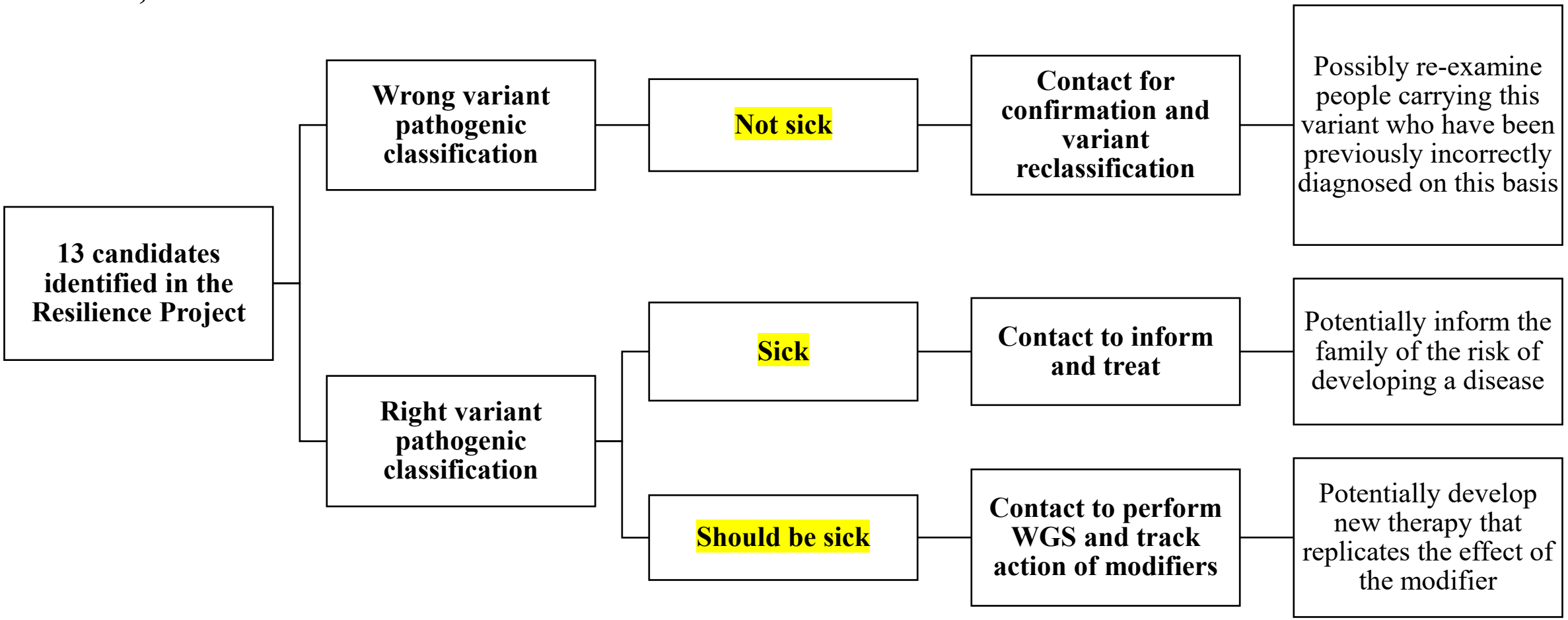
- A **modifier gene** is a gene that affects the expression of one or more genes (=**epistasis**).
- A **protective gene** is a modifier gene (= **epistatic gene**) whose action protects an individual from the harmful influence of a gene carrying a pathogenic mutation (= **hypostatic gene**).




TYLER-SMITH et al., Human evolutionary genetics (second edition), Garland Science, 2014, ISBN 978-0-8153-4148-2, page 46

# Relevant in all cases

**Not sick, sick or should be sick**




**Recontact? No re-contact possible (68% of the total cohort come from …23andMe!)**

# No re-contact possible

## 68% of the total cohort come from 23andMe

- 68% of the total cohort come from 23andMe
- 4 candidates out of the 13 identified come from 23andMe
- 23andMe did not foresee (at that time) the possibility that its customers on the direct-to-consumer DNA tests market could be re-contacted.

**Table 2 Data sources used in current retrospective study**

| Sample source | Sample type | Sample size | Technology |
|---|---|---|---|
| TCGA | Matched normal tissues for 17 tumor types | 4,114 | WES and WGS |
| Mount Sinai BioBank | Various diseases | 11,212 | Genotyping array |
| 23andMe | Mixed | 399,809 | Genotyping array |
| 1000 Genomes Projects | Healthy | 1,092 | Low pass WGS |
| ESP6500 | Various diseases | 6,503 | WES |
| UK10K[a] | Cohorts; neurodevelopmental disorders; obesity samples; rare diseases | 14,614 | Partly WGS, partly WES |
| SISu[a,b] | Case-control mixed | 3,325 | WES |
| FINN[a,c] | Case-control mixed | 11,693 | Genotyping array |
| CHOP-BGI | Case-control mixed | 699 | WES |
| CHOP | Case-control mixed | 96,007 | Genotyping array |
| BGI | Case-control mixed | 35,146 | Partly WGS, partly WES |
| SWE-SCZ | Schizophrenia cases and controls | 5,092 | WES |
| Total WES/WGS | | 70,585 | |
| Total genotyping | | 518,721 | |
| Grand total | | 589,306 | |

### Attempted recontact of candidate resilient individuals

We were unable to recontact any of the 13 candidate resilient individuals identified in this study, often due to the absence of a recontact clause in the original informed consent forms used for the studies from which these individuals were identified. Although recontact was possible for some cohorts in this study (e.g., Mount Sinai School of Medicine Biobank), no candidates were identified from those cohorts. Given this, we were unable to perform additional critical preprocessing steps to further confirm the resilient status of these individuals. Such steps would include confirming that the analyzed DNA matched the correct medical records for each individual, that they had not been diagnosed with the indicated Mendelian disorder, and that they were not mosaics. We consider these preprocessing steps as critical in order to formally characterize candidates as truly resilient.

**Table 4 13 Candidates identified in the Resilience Project**

| Phenotype | Gene | Mutation (cDNA; protein (reference)) | Genomic coordinate (hg19) | Mutation severity | Candidate confidence | Panel source | No. of candidates | Zygosity | Data source | Level of support for candidacy[a] | Sample status | Population carrier frequency[b] 1KG | Population carrier frequency[b] ESP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cystic fibrosis | *CFTR* | c.1558G>T; p.V520F (NM_000492.3) | Chr7 117199683 | Severe pulmonary disease, childhood-onset | Strong | Core allele panel | 3 | hom | 23andMe | C1,C2,C3, G1,G2,G3 | 2 adults, one declared no manifestation | 0.00 | 0.00 |
| Smith-Lemli-Opitz syndrome | *DHCR7* | c.964-1G>C (NM_001360.2) | Chr11: 71146886 | Severe developmental disorder, probably embryonic lethal | Strong | Core allele panel | 2 | hom | UK10K | C1,C2, G1,G2 | Not obtained | 0.0052 | 0.011 |
| Familial dysautonomia | *IKBKAP* | c.2204+6T>C (NM_003640.3) | Chr9: 111662096 | Severe neurological disease, high mortality in early childhood | Strong | Core allele panel | 1 | hom | 23andMe | C1,C2, G1,G2,G3 | No disease reported by individual | 0.00 | 0.0012 (only in EA) |
| Epidermolysis Bullosa simplex | *KRT14* | c.373C>T; p.R125C (NM_000526.4) | Chr17: 39742714 | Severe dermatologic condition, infantile onset | Strong | Core allele panel | 1 | het | BGI | C1,C2,C3, G1,G2 | No disease reported by individual | 0.00 | 0.00 |
| Pfeiffer syndrome | *FGFR1* | c.755C>G; p.P252R (NM_023110.2) | Chr8: 38282208 | Severe congenital skeletal dysplasia with variable expressivity | Strong[c] | Core allele panel | 1 | het | SWE-SCZ | C1,C2,C3, G1,G2,G3 | No abnormal morphology reported in discharged health information | 0.00 | 0.00 |
| APECED | *AIRE* | c.769C>T; p.R257* (NM_000383.2) | Chr21: 45709656 | Severe childhood-onset autoimmune disease | Strong | Core allele panel | 1 | hom | 23andMe | C1,C2,C3, G1,G2 | No disease reported by individual | 0.00 | 0.00015 |
| Acampomelic campomelic dysplasia | *SOX9* | c.1320C>G; p.Y440* (NM_000346.3) | Chr17: 70120318 | Severe skeletal dysplasia with early childhood death | Strong | Expanded panel | 1 | het | FINN | C1,C2, G1,G2 | Not obtained | 0.00 | 0.00 |
| Atelosteogenesis | *SLC26A2* | c.835C>T; p.R279W (NM_000112.3) | Chr5: 149359991 | Severe early-onset skeletal dysplasia with variable expressivity | Moderate[d] | Expanded panel | 3 | hom | 23andMe | C1,C2, G1,G2 | Not obtained | 0.0028 | 0.0023 |

[a]See **Table 5** for code definitions. [b]Carrier frequencies from combined ethnicities. [c]Individual was categorized as strong candidate due to lack of dysmorphic features. [d]Individual with variable phenotypes have been reported with the mutation[37].
EA, European American.

# Quest for modifiers

**Mimic nature's successful strategy**

- Prof. Riordan commented the Resilience Project as follows: "[T]*his work provides proof-of-principle that* ***individuals resistant to highly penetrant genetic diseases can be identified****, paving the way for mechanistic studies* ***to discover modifier genes that may be therapeutically manipulated to benefit susceptible individuals****"*

[RIORDAN J.D., NADEAU J. H., "*From Peas to Disease: Modifier Genes, Network Resilience and the Genetics of Health*" in *The American Journal of Human Genetics*, 101, 177–191, 3 August 2017, http://dx.doi.org/10.1016/j.ajhg.2017.06.004]

From Peas to Disease:
Modifier Genes, Network Resilience, and the Genetics of Health

Jesse D. Riordan[1,*] and Joseph H. Nadeau[1,*]

# CCR5

## Stephen Lyon Crohn and the “Berlin Patient”

Stephen Lyon Crohn, who, being a carrier of a **CCR5 gene mutation**, **was genetically immune to most forms of the AIDS virus**.

The **accidental discovery** of this mutation and its effects has **led to the development of new drugs (such as Maraviroc)**

> “*This mutation stopped HIV getting into his cells, but it had no adverse effect on his health. Scientists realized that CCR5 was an ideal drug target and a pharmaceutical that blocks it, maraviroc, is now used to help control the infection in some patients with the virus*”
>
> “*In 2007, a patient in Germany was effectively cured of HIV-1 infection after receiving bone marrow transplants from a donor who had the same mutation as Crohn. “Stephen’s participation helped this line of research several times. In medical research, participation by volunteers is critical. The fact that individuals like Stephen Crohn existed without CCR5 gave greater momentum to the development of inhibitors of CCR5”*”.

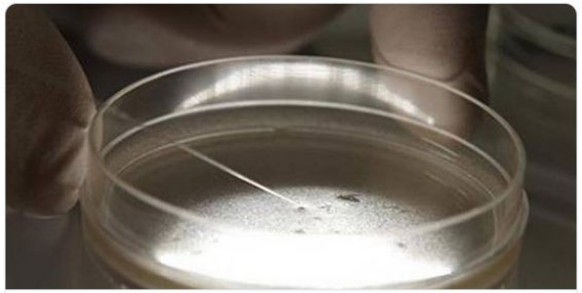
[Pincock S., “*Obituary – Stephen Lyon Crohn*”, The Lancet, 02 November 2013, https://doi.org/10.1016/S0140-6736(13)62279-5]

Antonio Regalado
@antonioregalado
Abonné

The Hindu reporting on a second "Berlin patient"-- i.e. a 2nd person cured of HIV infection via bone marrow transplant from a donor immune to HIV because lack working copies of CCR5 gene.

Removing CCR5 gene: also the goal of CRISPR baby experiment.

Traduire le Tweet



**HIV remission achieved through stem cell transplantation**
At present, this is possible only if people living with HIV also have some form of cancer
thehindu.com

12:59 - 4 mars 2019

# COVID HUMAN GENETIC EFFORT

"We're going to try to find the genetic basis of severe coronavirus infection in young people."

— Dr. Jean-Laurent Casanova, Co-Leader

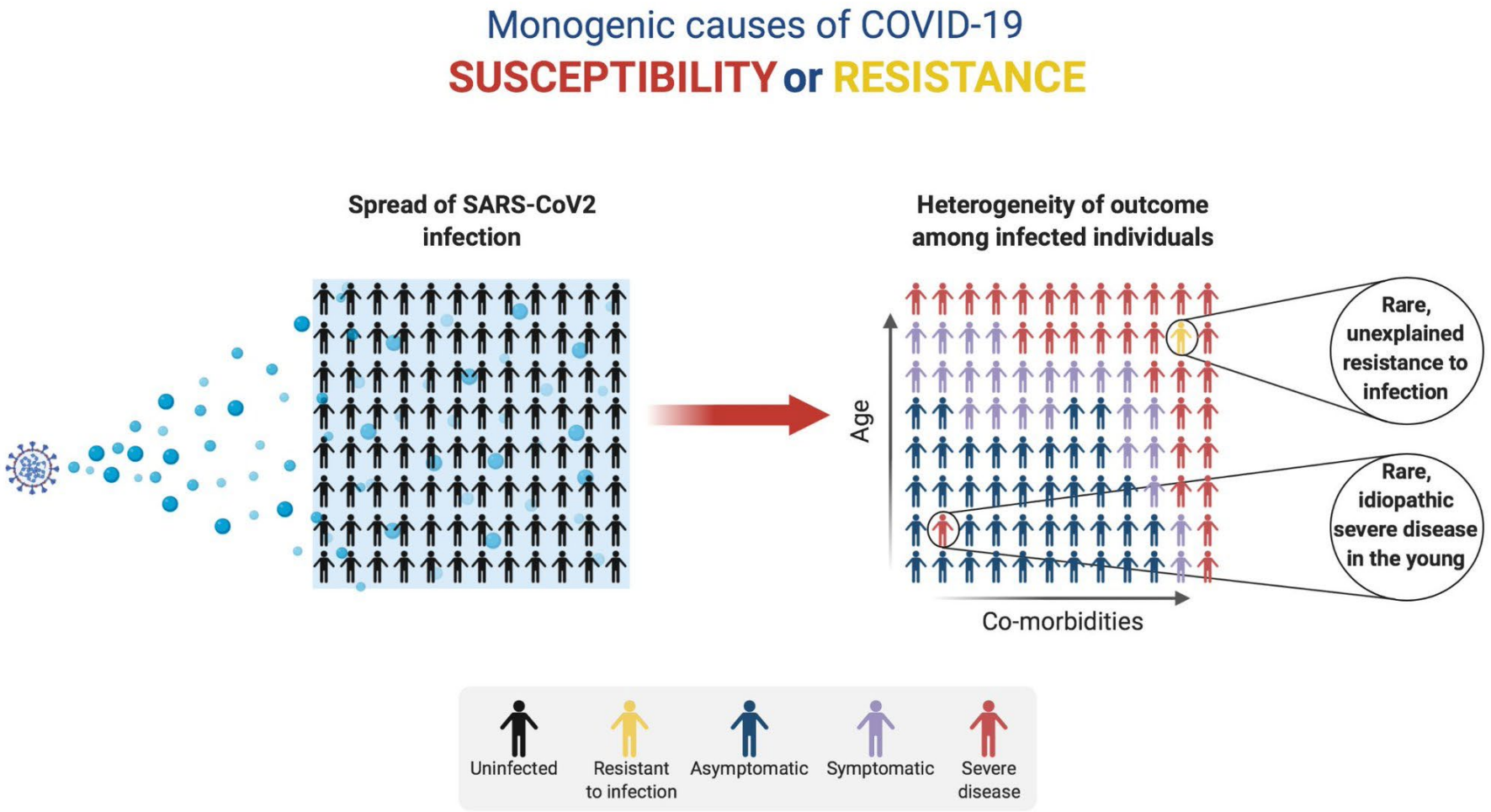
The Rockefeller University, Howard Hughes Medical Institute (HHMI), New York, USA

Necker Hospital for Sick Children & INSERM, Paris, France

| | Pathogen (condition) | Gene | Ref |
|---|---|---|---|
| **Resistance** | HIV | *CCR5* | [1-3] |
| | Norovirus | *FUT2* | [4] |
| | Plasmodium vivax | *DARC* | [5] |
| **Susceptibility** | Influenza virus (severe pneumonitis) | *IRF7* | [6] |
| | | *IRF9* | [7] |
| | | *TLR3* | [8] |
| | Rhinovirus (severe pneumonitis) | *IFIH1* | [9, 10] |
| | Herpes simplex virus 1 (encephalitis) | *UNC93B1* | [11] |
| | | *TLR3* | [12] |
| | | *TRIF* | [13] |
| | | *TRAF3* | [14] |
| | | *TBK1* | [15] |
| | | *IRF3* | [16] |
| | | *SNORA31* | [17] |
| | Viral brainstem encephalitis | *DBR1* | [18] |
| | Beta-papillomavirus (skin warts and cancer) | *EVER1* | [19] |
| | | *EVER2* | [19] |
| | | *CIB1* | [20] |
| | Alpha-papillomavirus (Juvenile-onset recurrent respiratory papillomatosis) | *NLRP1* | [21] |
| | Epstein-Barr virus (hemophagocytosis, lymphoproliferation, lymphoma, hypogammaglobulinemia) | *SH2D1A* | [22] |
| | | *XIAP* | [23] |
| | | *ITK* | [24] |
| | | *CD27* | [25] |
| | | *CD70* | [26, 27] |
| | Cytomegalovirus (disseminated disease) | *NOS2* | [28] |
| | Hepatitis A virus (fulminant hepatitis) | *IL18BP* | [29] |
| | Live-attenuated measles or yellow fever vaccine (disseminated disease) | *IFNAR1* | [30] |
| | | *IFNAR2* | [31] |
| | | *STAT2* | [32] |

https://www.covidhge.com/

# Covid Human Genetic Effort



# Quid for FBN1?

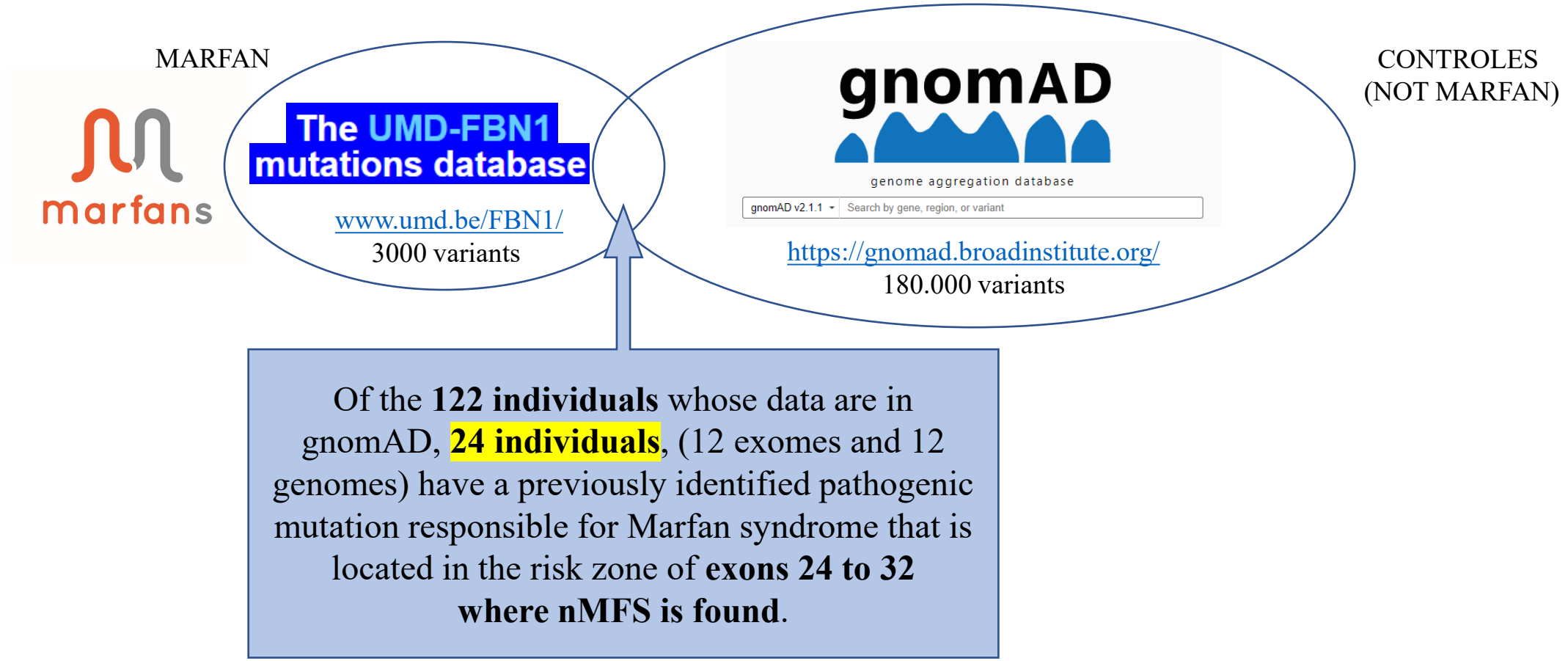
# Mimic nature’s successful strategy

**Professor Hal Dietz**

- The American *Marfan Foundation* has published on its website an interview with **Professor Hal Dietz** (The Johns Hopkins Hospital (Baltimore - USA) in which he explains that:
    - **the crossing of genomic and phenotypic data** could make it possible to understand “***how natural genetic variants can protect some people from the consequences***” of a pathogenic mutation and on this basis possibly be able to “***identify drugs that can mimic nature’s successful strategy***”.


WEISMAN R., "*Meet Your Gene: An Introduction to the Marfan Gene and Current Research*", 10 January 2017. Available at: http://blog.marfan.org/meet-your-gene-an-introduction-to-the-marfan-gene-and-current-research

# Data mining



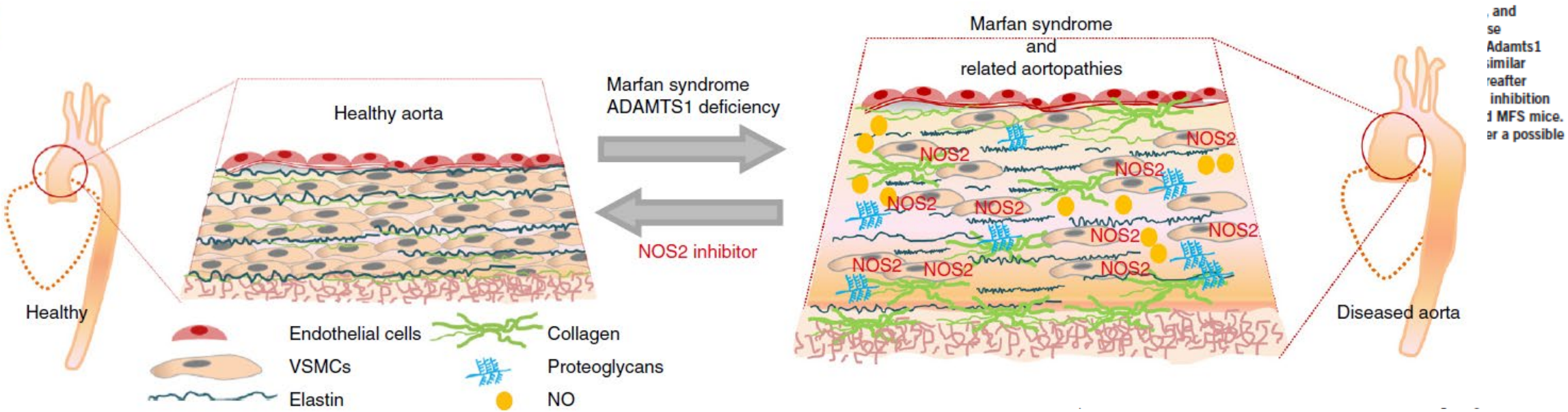

This observation was subsequently confirmed in the scientific literature in 2019. See BAUDHUIN L. ET AL., « *Variability in gene-based knowledge impacts variant classification: an analysis of FBN1 missense variants in ClinVar* », EJHG, 21 May 2019, https://doi.org/10.1038/s41431-019-0440-3.

# NOS2?

**2017**

## Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome

Jorge Oller[1,10], Nerea Méndez-Barbero[1,10], E Josue Ruiz[1], Silvia Villahoz[1], Marjolijn Renard[2], Lizet I Canelas[1], Ana M Briones[3], Rut Alberca[1], Noelia Lozano-Vidal[1], María A Hurlé[4], Dianna Milewicz[5], Arturo Evangelista[6], Mercedes Salaices[3], J Francisco Nistal[4], Luis Jesús Jiménez-Borreguero[7], Julie De Backer[3], Miguel R Campanero[8,11] & Juan Miguel Redondo[1,9,11]




OLLER, J. et a., « *Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome* », NATURE, published online 9 January 2017; doi:10.1038/nm.4266.

Considering that NOS2 inhibitors have been safely used in clinical trials for endotoxemia, rheumatoid arthritis and migraine (https://clinicaltrials.gov/ct2/home identifiers: NCT00184990, NCT00370435 and NCT00242866), our results point to NOS2-specific inhibitors as a promising alternative for the treatment of aortic disease that could be implemented with minimal delay.

# A missing resource

## Fondation 101 Génomes

My wife and I then realized that:

- That there was **hope of discovering a modifier gene for FBN1**.
- **That the researchers did not have the necessary tools to conduct this research**.

**We therefore decided to make the missing resources available to all scientists.**

**And to do so, we created the "*Fondation 101 Génomes*"**

Fondation 101 Génomes

Genomics for Rare Diseases

101 Genomes Foundation
Genomics for Rare Diseases

King Baudouin Foundation
*Working together for a better society*

# Fondation 101 Génomes

FONDATION PRIVÉE

**WHITE PAPER:**

**101 GENOMES FOUNDATION** *FONDATION PRIVÉE* **&**

**PROJECT 101 GENOMES MARFAN**

*(VERSION 7 – 03/12/2018)*



# 101 Genomes

# *Unique and unprecedented example*

**Professor Anne De Paepe**

- The **101 Genomes Foundation (F101G)** aims **to advance research** through the creation of **an innovative genomic biobank** that will allow researchers to better understand and treat rare disease**s**.
- **The disruptive innovation** of the **genomics and bioinformatics revolution** makes this objective possible today.

According to Professor Anne De Paepe, ProRector of Ghent University, this is "*a unique and unprecedented example of* ***patient participation in scientific research***".

# Pilot project

## 101 Genomes Marfan Project

- **The 101 Genomes Marfan Project (P101GM) is the pilot project of the F101G**. This Project is dedicated to **Marfan syndrome.**
- It is built on an extensible starting cohort of **101 patients**.
- The creation of the **Genomic Cloud** is an integral part of this pilot project.
- When the **Genomic Cloud** is set-up it will be able to host **other projects dedicated to other rare diseases** that will benefit from the experience gained.






# Scientific Committee

- **The P101GM Scientific Committee** is composed of **leading scientists in Marfan Syndrome and algorithmics**.
- Among the members of the committee are the professors **Julie De Backer, Bart Loeys, Guillaume Smits, Guillaume Jondeau, Catherine Boileau** and **Anne De Paepe.**
- The Committee is **co-chaired** by **Julie De Backer** and **Bart Loeys**
- **They conduct the GEMS project**

# Cooperation
## & European Associations

**DECLARATION OF COOPERATION**

**TO THE 101 GENOMES PROJECT DEDICATED TO MARFAN SYNDROME**

**OF THE 101 GENOMES FOUNDATION**

**BETWEEN**

**The 101 Genomes Foundation** (F101G) was founded in November 2017. Its objective is to advance research by 10 years by creating a bioinformatics database containing complete genomic (Whole ypic cross data of patients with rare diseases. This tool, which is community through a secure interface, aims to help improve e F101G pilot project is dedicated to Marfan syndrome. This is the reinafter P101GM);

The P101GM is supported by **several European Marfan patient associations**:

- **Belgian Marfan Syndrome Association;**
- **French Marfan Syndrome Association;**
- **den-i (Luxembourg);**
- **…**

# 101 Genomes Marfan Project, 101 Genomes Foundation & 101 Genomes Fund @FRB


1. **The 101 Genomes Marfan Project (P101GM) (= GEMS)** is the pilot project of:
2. **The 101 Genomes Foundation (F101G),** which can potentially host parallel projects relating to other rare diseases. The sums necessary for the implementation of the bioinformatics tool are collected on:
3. **The 101 Genomes Fund** co-managed by the King Baudouin Foundation and the 101 Genomes Foundation.

**This architecture** was drawn with the **King Baudouin Foundation** that emphasized the need to foreseen the possibility to extend **the bioinformatics tool** set up to study Marfan syndrome **to other rare diseases.**

# Organigram

King Baudouin Foundation
*Working together for a better society*

101 Genomes Fund

**President**: Dr Michel Verboogen
**Vice-President**: Cécile Jacquet
**Secretary**: Ludivine Verboogen
**Treasurer**: Romain Alderweireldt
**CEO in the daily Management**: Ludivine Verboogen

Fondation 101 Génomes
Genomics for Rare Diseases

**Management Committee**

**President**
Prof. Anne De Paepe (UZGENT)

**Members**

Gerrit Rauws
Ludivine Verboogen
Romain Alderweireldt
*Secrétaire:*
Annemie T'Seyen

**Scientific Committee**

**Co-Presidents**
Prof. Julie De Backer (UZGENT)
Prof. Bart Loeys (UZA)

**Members**
Prof. Anne De Paepe (UZGENT)
Prof. Catherine Boileau (APHP)
Prof. Guillaume Jondeau (APHP)
Prof. Guillaume Smits (ERASME)
Prof. Tom Lenaerts (ULB/VUB)
Dr. Aline Verstraeten (UZA)
Prof. Paul Coucke (UZGENT)

European Reference Network
for rare or low prevalence complex diseases
Network Vascular Diseases (VASCERN)

101 Genomes Marfan

GEMS App

marfans

ABSM

den-i.lu
syndrome de Marfan

RaDiOrg
RARE DISEASES BELGIUM

[RaDiOrg stelt met trots de laureaat 2018 van de Edelweiss Award voor]

It received the **2018 Edelweiss Award** from the Belgian alliance for rare diseases: RaDiOrg


## RaDiOrg stelt met trots de laureaat 2018 van de Edelweiss Award voor

2 mei 2018 by Eva Schoeters

***Patiëntenorganisatie ABSM, die zich inzet voor patiënten met het Syndroom van Marfan, nomineerde Romain Alderweireldt voor de Edelweiss Award omwille van zijn innovatieve ideeën en zijn doorzettingsvermogen.***

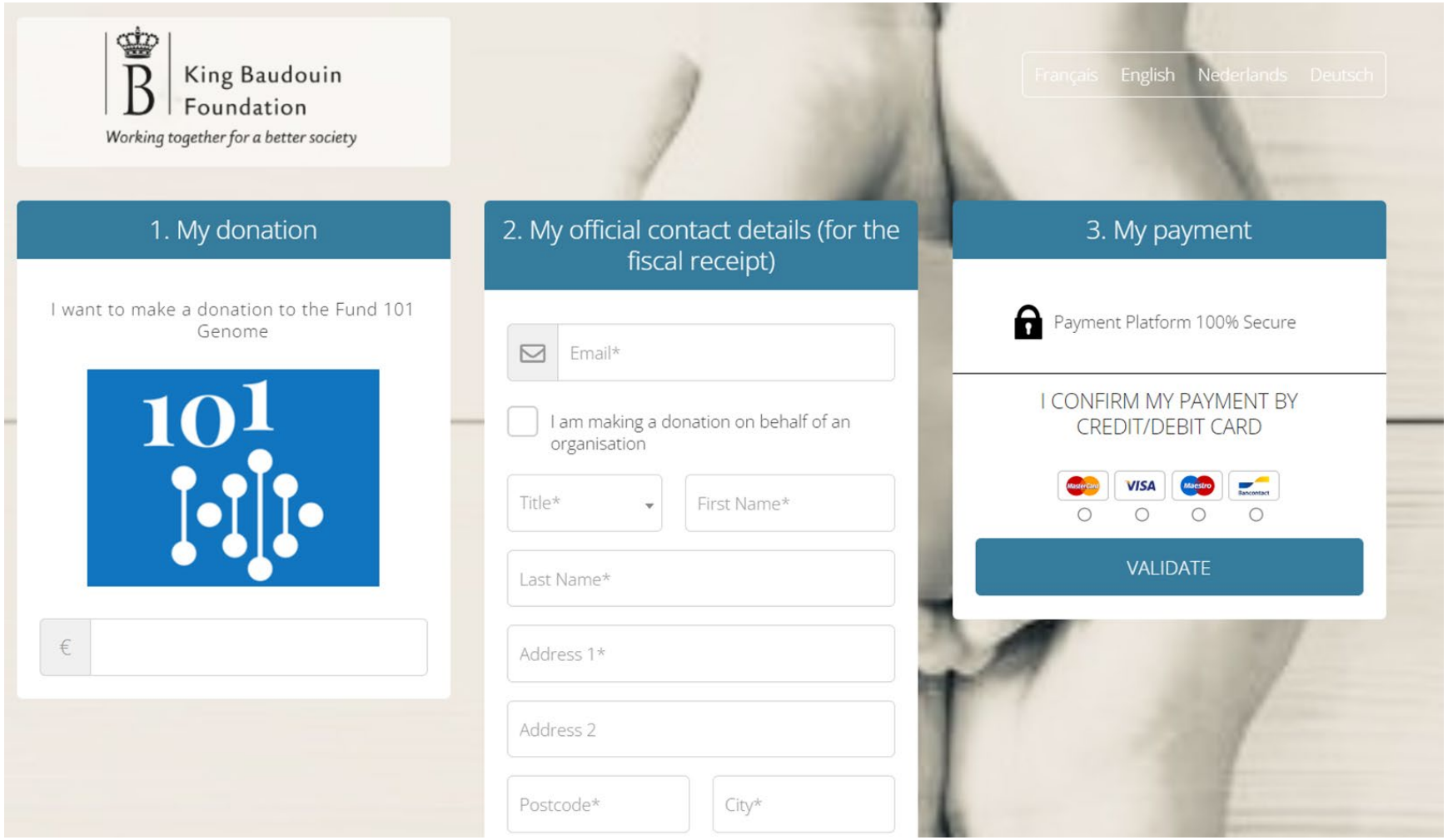
Na de diagnose van zijn zoon, heeft hij zich ingewerkt in de wetenschappelijke literatuur en nam hij contact op met verschillende specialisten. Na heel wat discussies en ontmoetingen met deze onderzoekers van over de hele wereld, creëerden Romain en zijn echtgenote de "Stichting 101 Genomen". Dit is een cross-databank die de genomische en fonotypische gegevens van patiënten met zeldzame ziekten verzamelt. Daarnaast maakt Romain deel uit van de Raad van Beheer van ABSM en vertegenwoordigt hij de vereniging bij de Europese Referentienetwerken (ERN).

# Fundraising

101 Genomes Foundation
Genomics for Rare Diseases

King Baudouin Foundation
*Working together for a better society*

[Make a gift (kbs-frb.be)]



101 Genomes Foundation
Genomics for Rare Diseases

King Baudouin Foundation
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[Make a donation | Koning Boudewijnstichting (kbs-frb.be)]

# Recognition and agreements with the King Baudouin Foundation in Europe

Donors established in **France**, the **Netherlands**, the **Grand Duchy of Luxembourg** and **Denmark** who wish to support an initiative or a fund managed by the King Baudouin Foundation can make their donations directly to the King Baudouin Foundation while also benefitting from the tax advantages of their own country of residence. We take charge of issuing the relevant tax certificates for the countries concerned.

'Friends of' funds, project accounts, cultural sponsorship accounts for the performing arts/museums and solidarity accounts for schools with donors based in Europe are invited to use the Transnational Giving Europe network.

In France, the King Baudouin Foundation obtained in 2022 a prolongation of the various tax agreements set out in 4b of Articles 200, 238 b and Articles 978 and 795-0 A of the General Tax Code.

In the Netherlands, the King Baudouin Foundation has been recognised as ANBI (Algemeen Nut Beogende Instelling - a public benefit organisation) since January 1st 2008. Our RSIN number is 8237.85.385.

In the Grand Duchy of Luxembourg, following the Tax Director's circular L.I.R. - n°112/2 , and in Denmark, according to the Danish Tax Assessment Act - Ligningslovens § 8A od 12, stk.3, the King Baudouin Foundation is also authorised to issue tax receipts to resident donors.

## Transnational Giving Europe

The Transnational Giving Europe (TGE), (TGE) network, coordinated by the King Baudouin Foundation, enables you to make a cross-border donation to projects in **20 countries of Europe**, as well as to benefit from a tax reduction on any donation of 40 euros or more. Organisations and associations in Belgium may also collect donations made in other European countries. Donations made by European donors are tax deductible, in line with the legislation operating in the relevant countries.

## King Baudouin Foundation United States (KBFUS)

Donors residing in the USA can very easily support us via the KBFUS. An American philanthropic organisation that is part of the KBF 'family', KBFUS enables American donors to make donations to projects in Europe and Africa, while still benefitting from tax-reductions in the USA./p>

## King Baudouin Foundation Canada (KBF CANADA)

Donors living in Canada can also easily support us through KBF CANADA. . As another member of our 'family', this Canadian philanthropic organisation enables Canadian donors to support projects in Europe, Africa, America and Asia. KBF CANADA is authorised to issue tax receipts for Canadian donors.

## Give2Asia

As an American charitable organisation, Give2Asia is a facility for American donors who wish to support charitable organisations in 23 countries of Asia. Give2Asia Foundation Ltd facilitates cross-border donations from Hong Kong SAR. Give2Asia Australia, on the other hand, serves donors based in Australia.

101 Genomes Foundation
Genomics for Rare Diseases

King Baudouin Foundation
*Working together for a better society*

## Invitation "One day, one night..."

2019

Dear
Octob
Forte
Mrs F


## Theatrical improvisation show of the company Motamo

2019

On March 14th, more than 130 spectators attended the Tartine à Lasne, a theatrical improvisation show by the Motamo company organised to benefit the F101G. Vincent Verboogen, Ludivine's brother, organized a theatrical improvisation show to benefit Fondation 101 Génomes. This show was given in Lasne (France) and [...]

## On May 6, 2018, run the 10km of Uccle with the F101G!

F101G RUN, 2018

Dear All, a huge thar
was a great first for
and pleasure to be t

Share:

Customize buttons

## "Genome and Medicine: Conquests and Frontiers" by Prof. Alain Fischer, 29 March 2019

2019

The Fondation 101 Génomes and Delen Bank organized with the invaluable help of Professor Michel Goldman a Conference evening on Friday 29 March 2019 at the Brussels headquarters of the Bank. At this evening, Professor Anne de Paepe, Pro-Rector of the University of Ghent and President of the Fonds 101 Génomes at the Fondation ROI Baudouin [...]

Fondation 101 Génomes
filigranes
LIBRAIRIE 365→365
Genomics for Rare Diseases


## Filigranes evening with Philippe Geluck for the benefit of the Fondation 101 Génomes

2021

On 29 November 2
101 Génomes (F101
authors. During thi
receipts of the bar


Dec 15

**Dégustation de vins espagnols**

Dégustation de vins espagnols au profit de la Fondation 101 Génomes le samedi 15 décembre 2018 de 15 à 21h

By Fondation 101 Génomes

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impatients!

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BONJOUR ROMAIN

# Les impatients!

51 137 € récoltés

New Research on rare diseases.
Now!

***https://www.theimpatients.org/***

impatients!

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HOME › THE IMPATIENTS! › PAGES

Find a page

ALL PAGES

**IMPATIENTS, ... et vous ?**

Raised 4 650 € Goal 4 200 €

**Thomas Carton - Forza**

Raised 200 € Goal 850 €

**Une faute de frappe dans mon génome**

Raised 4 020 € Goal 4 200 €

**Research for rare diseases now!**

Raised 3 450 € Goal 3 600 €

**Je suis impatient**

Raised 3 050 € Goal 3 200 €

**Ensemble, faire avancer la recherche**

Raised 2 900 € Goal 3 000 €

**Un nouvel espoir**

Raised 2 455 € Goal 2 600 €

**Me ayudas?**

Raised 2 310 € Goal 3 000 €

impatients!

LOG IN FR

HOME › THE IMPATIENTS!

# Cuento contigo / I need your help / J'ai besoin de vous !

by Isabel Cangas


**2 020 €** raised Goal **2200 €**

I DONATE I SHARE

100% safe

DONATIONS (23)

**23** magic donors are supporting **"Cuento contigo / I need your help / J'ai besoin de vous !"**

**50 €** Julien — 3 years ago
Feliz Navidad! J'espère que notre effort collectif permettra aux chercheurs de mieux comprendre les maladies rares pour mieux les guérir.

**300 €** Esther — 3 years ago
Buena iniciativa ¡mucho ánimo!

**50 €** Anonymous — 3 years ago
Buen proyecto. Ánimo!

**50 €** Alejandra — 3 years ago
familia :)

(Texte en FR, plus bas) (EN text below)
Hace dos años descubrimos que mi nieta padece una enfermad rara que afecta al tejido conectivo, en particular su corazón, sus huesos y articulaciones. Es una enfermedad grave, que requiere un seguimiento médico regular, que le permita tener un desarrollo lo mejor posible y evitar lo peor.

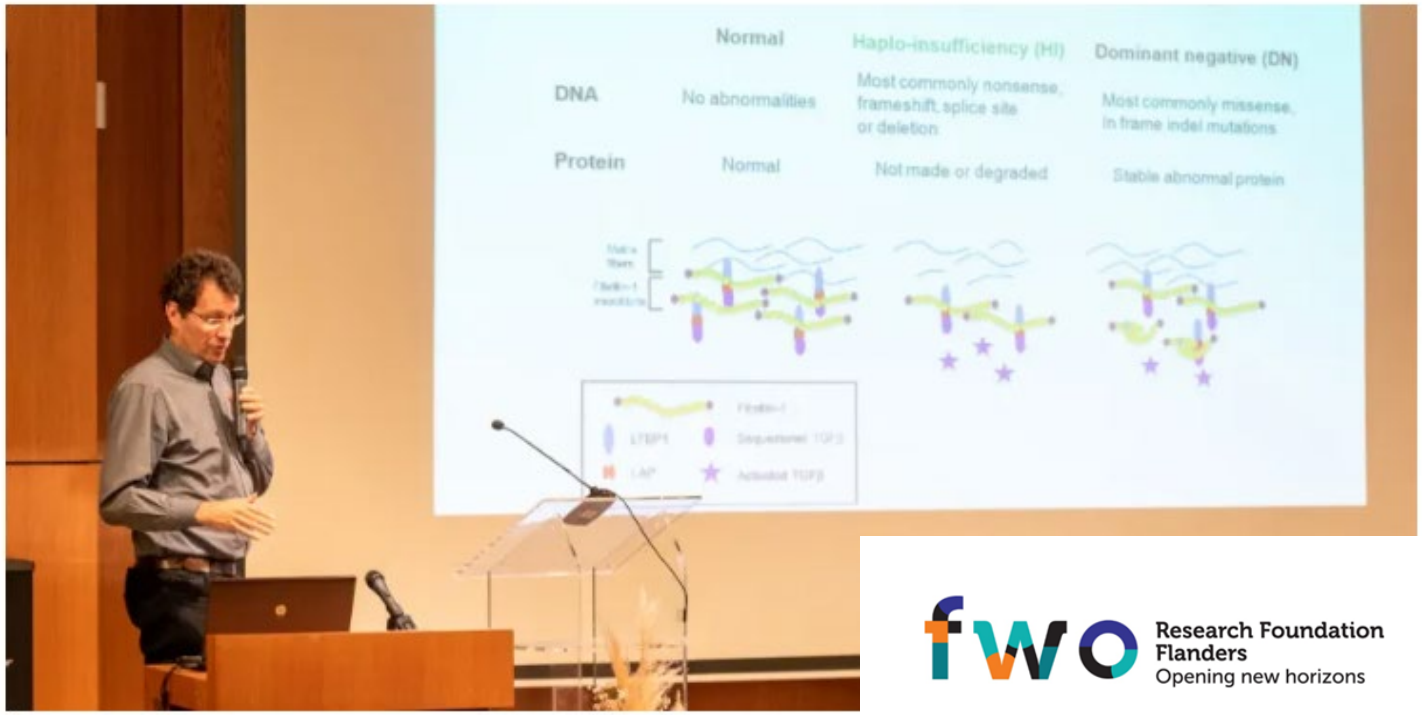
Aún no se sabe por qué esta enfermedad afecta con distintos grados de gravedad a las personas que la padecen. Para averiguarlo es necesario desarrollar una base de datos bio informática que, con la ayuda de la inteligencia artificial y la revolución genómica, permitirá acelerar el

[GEMS | A generous donor doubles up to 75.000 euros of donations for the GEMS project! - 101 Genomes Foundation (f101g.org)]

# GEMS | A generous donor doubles up to 75,000 Euros in donations for the GEMS project!

2020, GEMS / WEDNESDAY, DECEMBER 30TH, 2020

*On October 26, 2020, Fondation 101 Génomes signed an agreement of* ***"Matching Gifts"*** *with a partner who wishes to fund the GEMS project* ***up to 75,000 euros*** *over three years. This partner will therefore double all donations made to Fondation 101 Génomes for GEMS research over three years.*




[GEMS | 700,000 Euros for the quest for protective genes - 101 Genomes Foundation (f101g.org)]

# GEMS | 700.000 euros for the quest for protective genes

2020, GEMS / WEDNESDAY, DECEMBER 30TH, 2020

**700,000 euros to finance the Ghent & Antwerp teams working on GEMS!**

*On December 16, 2020, Professors Bart Loeys and Paul Coucke have both received more than 700,000 euros in funding. from Wetenschappelijk Onderzoek Fund (FWO) to work in the laboratory on the F101G flagship project: **the GEMS project!** It's fantastic!*


[Ludivine Verboogen et Romain Alderweireldt | Innoviris]


FBN1, anchor and
exploration point

# GEMVAP+

**Improve clinical diagnosis of rare genetic disorders with a GEne-specific Missense VAriant Predictor framework**

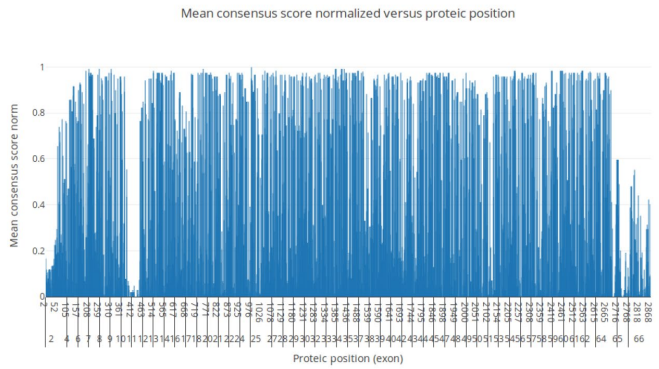
Missense variant interpretation is challenging

DNA HAS ALL YOU CAN ASK FOR .
DNA HAS ALL YOO CAN ASK FOR .

DNA HAS ALL YOU .
DNA HAS ALY OUC ANA SKF OR

DNA HAS ALL LOU CAN ASK FOR .

GEMVAP FBN1 top5 whole gene prediction




Interuniversity Institute of Bioinformatics in Brussels

ULB Center of Human Genetics

MLG MACHINE LEARNING GROUP


## "Artificial Intelligence (AI) for the diagnosis of Marfan Syndrome" by Professor Guillaume Smits

ABSM 20 GALA, 2019

Professor Guillaume SMITS, Université Libre de Bruxelles, member of the Scientific Committee of the 101 Genomes Marfan Project, explains the "GEne specific Missense VAriant Predictor (GEMVAP)" tool developed thanks to F101G and the role of artificial intelligence in the diagnosis of Marfan syndrome at the Gala des 20 ans [...]

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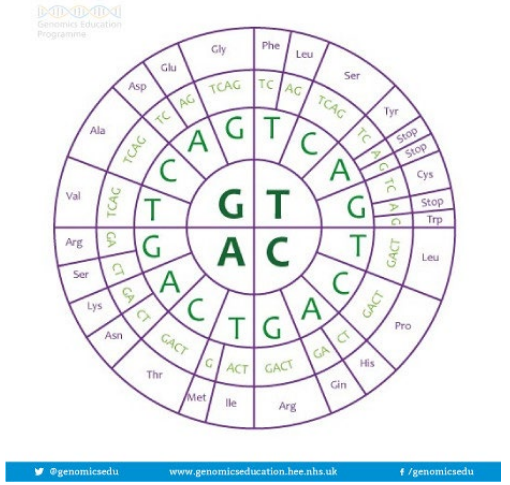
empowering research

# Genome4Brussels

## Gemvap (1/3)

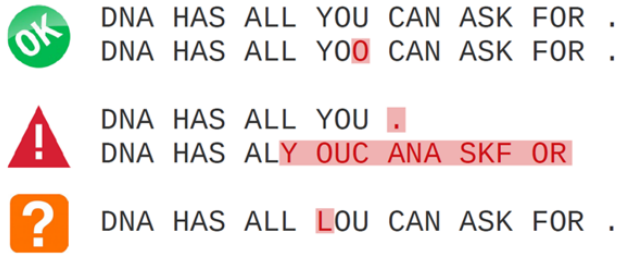
- **Chromosome 15 - FBN1 gene:** Reference sequence of **8,616 nucleotide positions (*np*)**.
- **Setting up the "chessboard":**
  - **There are only four nucleotide** possibilities (A, C, T, G) for each position (np). There is therefore a 'finite' set of 34,464 (=8,616 (np) *4) theoretical possibilities for the FBN1 gene
  - **Reference:** of these possibilities, 8,616 positions are those of the reference nucleotides that allow the production of the protein in the normal way.
  - **Synonymous variants:** of these possibilities, 4,636 are "synonymous variants" that will have the same impact on protein production as the reference nucleotide

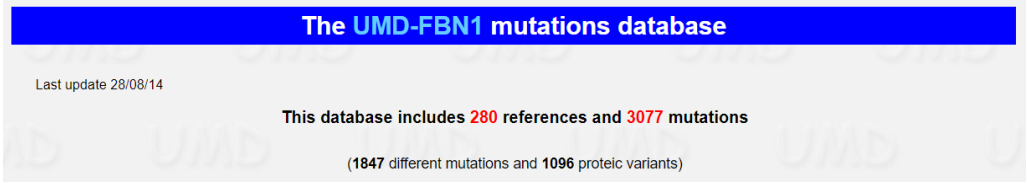


# Genome4Brussels

## Gemvap (2/3)

- **"Chessboard:**
  - **This leaves 21,212 (= 34,464 - (8,616 + 4,636)) variants** (positions / "*squares on the board*") to be classified as benign, pathogenic or SIV:
  - Of these 21,212 "theoretical" variants, less than **4,000 variants** have been observed in the real world by scientists and physicians and reported in scientific publications and/or in genetic databases such as UMD-FBN1, gnomAD, etc.




gnomAD
genome aggregation database

https://gnomad.broadinstitute.org/

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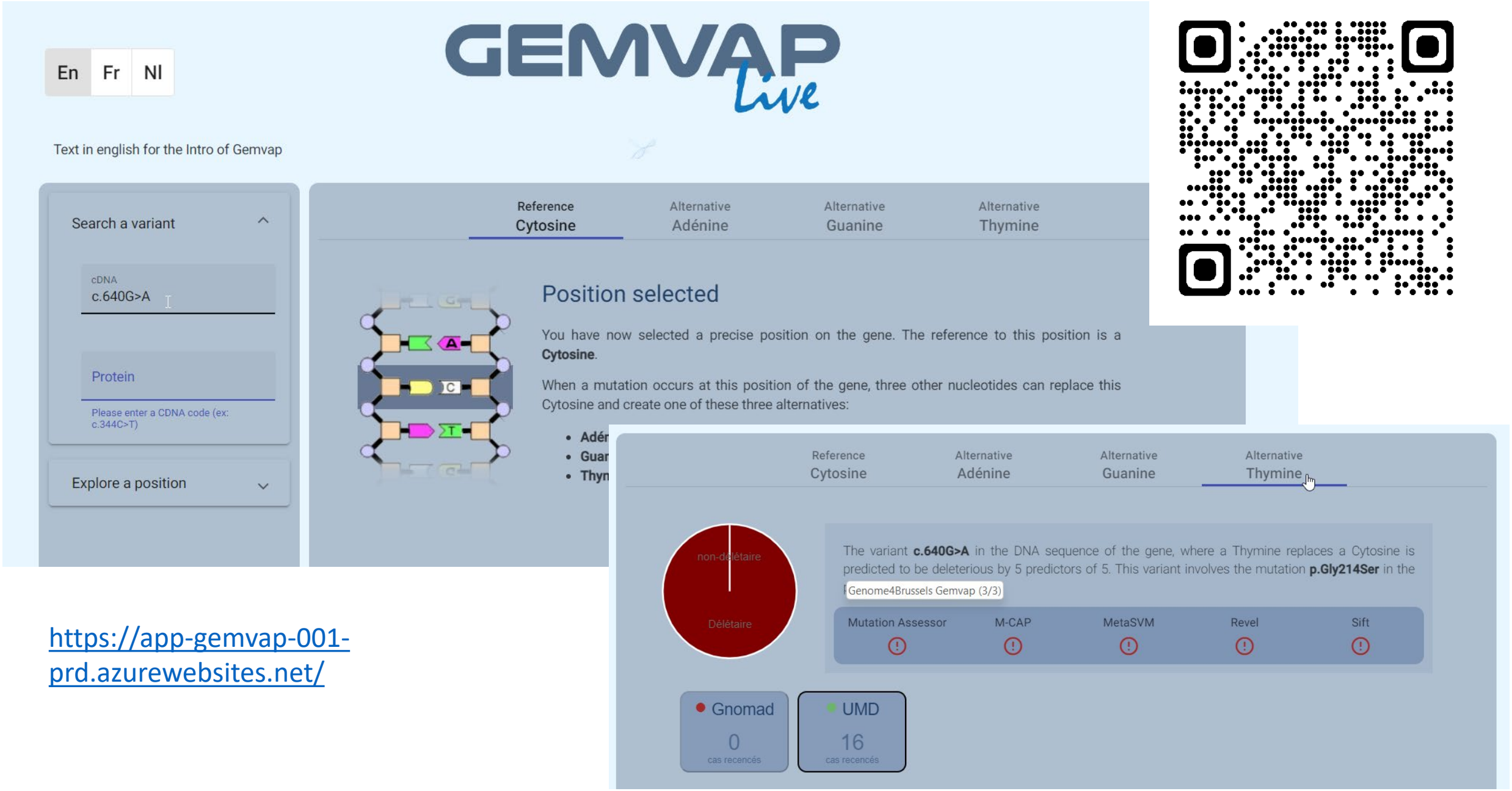
# Genome4Brussels

## Gemvap (3/3)


"Artificial Intelligence (AI) for the diagnosis of Marfan Syndrome" by Professor Guillaume Smits

- **Use of AI tools on the "*chessboard*":**
  - **Predictors:** For each of these 21,212 variants, we used more than 20 different "predictor" programs that predict the impact of a variant on the structure of the protein (the "*key*") and its ability to be functional (i.e. to "*fit properly into the corresponding lock*").
  - **Machine learning was** then used to select the five predictors for each "box" that provided the most accurate prediction of all the predictors.
  - **New classification:** Together, these bioinformatics tools produce an aggregate of results that provides the best classification for every conceivable variant.




https://app-gemvap-001-prd.azurewebsites.net/

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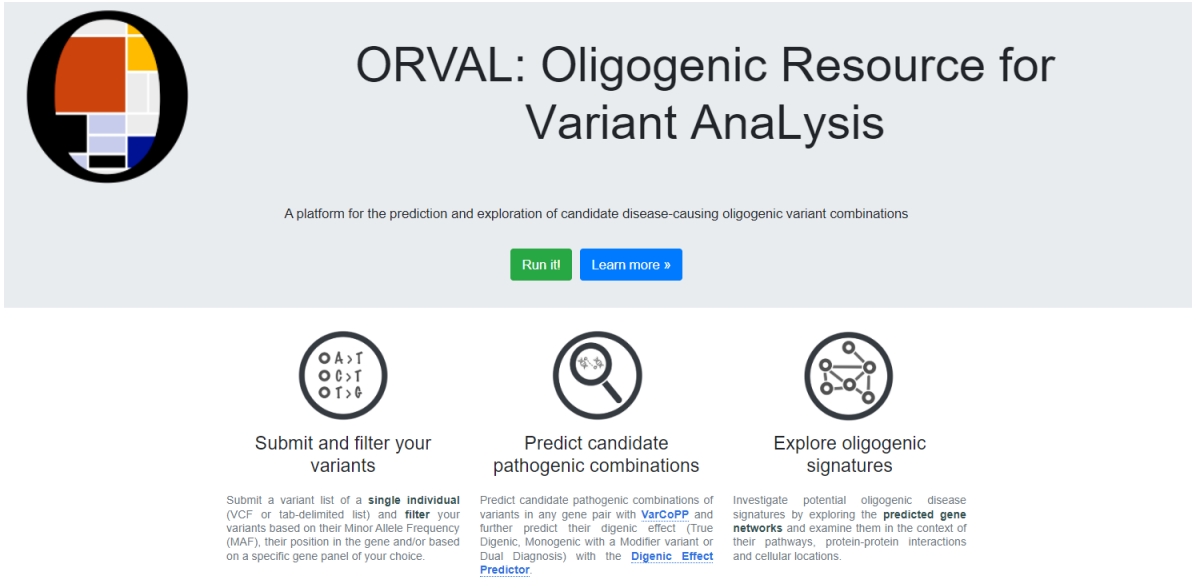
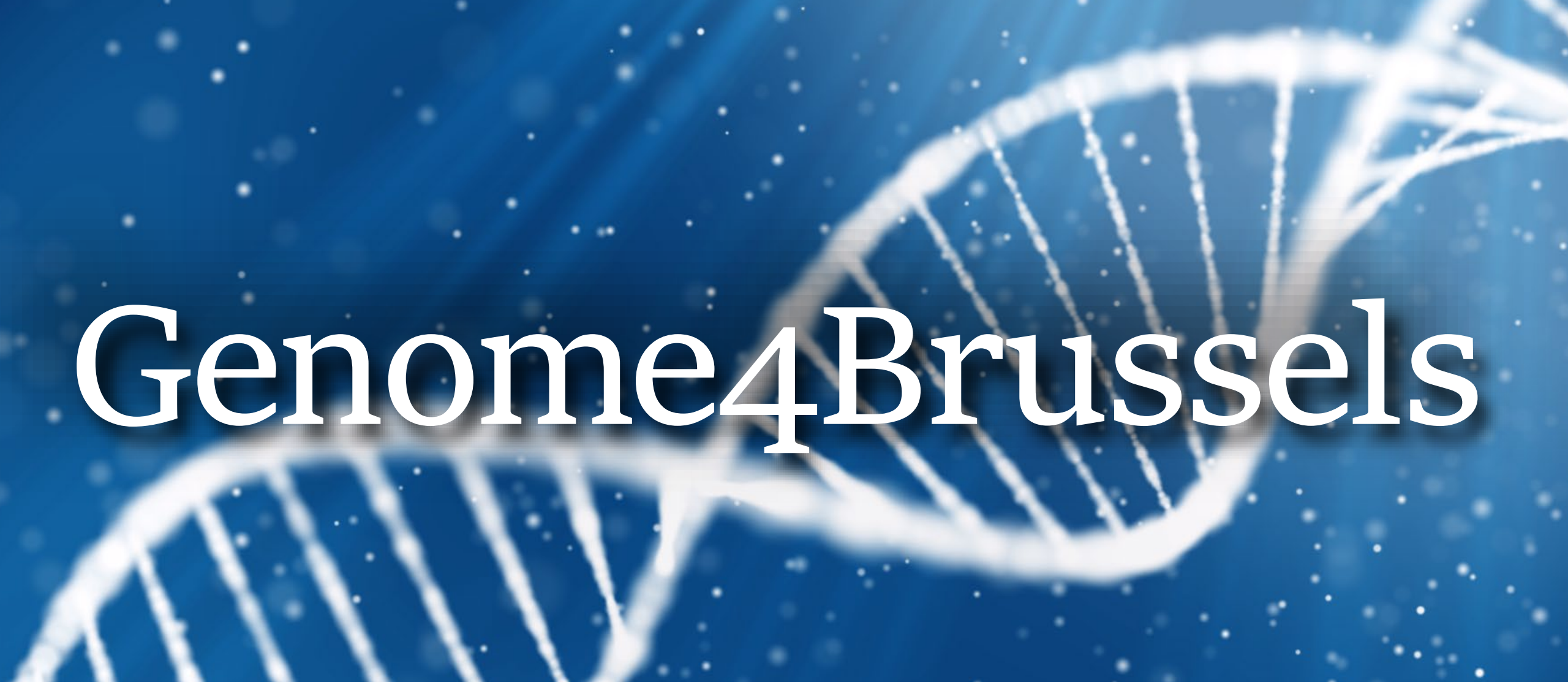
# Genome4Brussels

## Orval



- **Results :**
  - **Diagnostic aid**: Doctors who need to make a diagnosis on a mutation observed in the FBN1 gene can use this tool to make an initial classification and speed up their diagnosis.
  - **Gene network:** Once a pathogenic variant is confirmed, the tool is combined with other AI-based tools to identify gene networks and the extent of their interactions.






MLG
MACHINE LEARNING GROUP

B²
INTERUNIVERSITY INSTITUTE OF BIOINFORMATICS IN BRUSSELS

101 Genomes
Foundation
Genomics for
Rare Diseases

fair
genomics

funded by
innoviris
.brussels

# Genome4Brussels: AI, Genomics & Rare Diseases

GEMVAP, 2021, G4BXL / MONDAY, MAY 31ST, 2021

In 2019, the 101 Genomes Foundation, the *Interuniversity Institute Of Bioinformatics Brussels* (IB2), the *ULB Center of Human Genetics* (CHG) and the *ULB Machine Learning Group* (MLG) participated in a call for projects launched by Innoviris with the "Genome4Brussels" project. Within the framework of this project, they decided to create together an ecosystem that will optimise the development of bioinformatics tools for genome analysis and facilitate the transfer of the innovation and knowledge acquired during the project to the public.

## Project

**Genome4Brussels**. Genome4Brussels is a joint project that aims to create an ecosystem in the Brussels region that combines :

- optimal conditions for hosting and sharing genomic data led by patient representatives (Fondation 101 Génomes);
- medical and genomic expertise (CHG-IB2) and ;
- expertise in bioinformatics and artificial intelligence/IA (IB2-MLG).

This ecosystem will allow the emergence of a research platform dedicated to the development of bioinformatics tools developed through "transparent" AI (White Box) to assist physicians and researchers in the field of rare diseases.

In the framework of the Innoviris call: a research platform is set up, two bioinformatics tools are developed and the conditions for transferring these technologies to the public are created.

## Partners

**101 Genomes Foundation**. In 2017, the 101 Genomes Foundation embarked on a quest to find genomic superheroes whose genes protect them from the effects of certain rare diseases. To carry out this quest, Fondation 101 Génomes is starting by developing a database from which scientists can explore the human genome for protective (or aggravating) genes that explain the variability of rare diseases. Such a discovery would provide better diagnoses and allow for new treatments that replicate the protective (or limit the aggravating) effects identified. The 101 Genome Foundation's pilot project is dedicated to Marfan syndrome. This pilot project is supported by several European patient organisations and is led by leading scientists.

**IB2-CHG**. L'*Interuniversity Institute Of Bioinformatics Brussels* (IB2) and the *ULB Center of Human Genetics* (CHG) are jointly dedicated to the study of rare diseases. Their common mission is to improve the diagnostic quality of genetic tests, in order to improve clinical follow-up, treatment and therapeutic advice. Their research areas are part of this overall objective, and consist of identifying the genetic origin of rare diseases that are still insufficiently understood. IB2 and CHG are developing bioinformatics tools to explore and analyse patients' genomic data in an innovative way and thereby improve the quality of genetic/genomic testing.

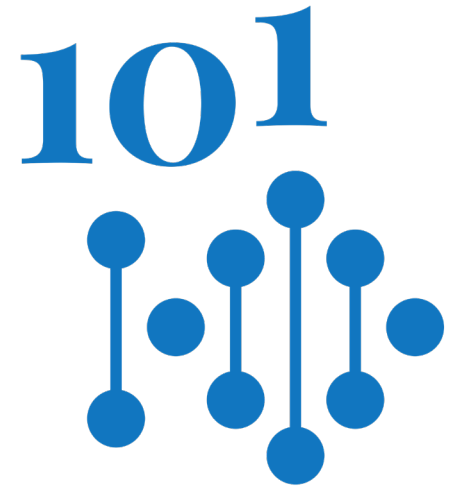
**IB2-MLG**. L'*ULB Machine Learning Group* (MLG) specialises in computer science, artificial intelligence, bioinformatics, computational biology, genetics, molecular biology and medicine. In the medical context, IB2 and MLG use methods associated with statistical scores that create a transparent "White-Box" model providing explanations of the decision made by the bioinformatics tools they develop with AI. It is indeed unthinkable to be satisfied with a basic AI approach (which provides results without a "Black-Box" explanation) in the context of the development of bioinformatics tools intended to assist clinicians.

**Fair Genomics (FairGX)**. In the course of the procedure, Innoviris asked the consortium to set up the *Fair Genomics* to accompany the project and, in so doing, enable a transfer to citizens of the technologies and innovation developed through Genome4Brussels. *Fair Genomics* is wholly owned and controlled by Fondation 101 Génomes .

**Ecosystem**. The partners intend to set up a virtuous circle to fuel and fund research and advance science.

Genome4Brussels: AI, Genomics & Rare Diseases - 101 Genomes Foundation (f101g.org)

# PART 2
# GEMS, Genomic Cloud and bioinformatics tools




GEMS App

# GEMS

## 'Our' GEMS

- GEMS is the **acronym** of ***Genome-wide Epistasis for cardiovascular severity in Marfan Study***
- The **objective** of GEMS is to identify protective modifier genes (= epistatic genes) within the whole human genome that can explain the variability of cardiovascular disease found in people with Marfan syndrome. Such a discovery would make it possible to contemplate new therapeutic approaches that would replicate the protective effects identified in order to prevent cardiovascular events
- **This research is at the heart of the Fondation 101 Génomes's action**. It is led by **Professor Bart Loeys** and the entire scientific committee of the Project 101 Genomes Marfan
- It is actively supported by the **VASCERN Network dedicated to vascular diseases** and by the main members of the HTAD group within it.

"An evocation of current research and future perspectives" by Professor Bart Loeys

ABSM 20 GALA, 2019

Professor Bart LOEYS, University of Antwerp & Co-Chair of the Scientific Committee of the 101 Genomes Marfan Project, presents the state of research initiated by the action of F101G: Genome-wide Epistasis for cardiovascular severity in Marfan Study (GEMS) and its vision for the future at the Gala des 20 ans de [...]

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# GEMS

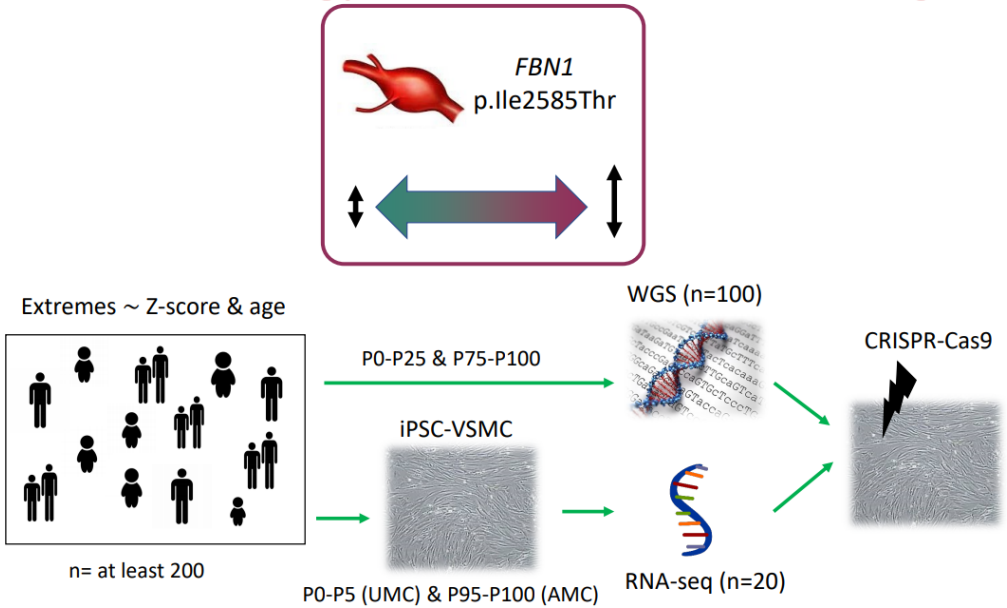
## Genome-wide Epistasis for cardiovascular severity in Marfan Study

UZA

UZ GENT

Research Foundation Flanders
Opening new horizons

### 3. Methodology: identification of modifier genes




**Cohort of over 260 carriers** of the two selected mutations.

**21 Reference Centers** are following the patients eligible for the investigation cohort.

# GEMS

## 262 patients!

Antwerp, Ghent, Leiden, Nijmegen, Groningen, Amsterdam, Paris, London, Hamburg, Sheffield, Zurich, Milan, Pavia, Bologna, Barcelona, Rome, Vienna, Umea, Ottawa, Baltimore, …

**26 Centers of reference** responded to the request of the GEMS project so far. (See ANNEXE 1: List with precise addresses)

**21 Centers of references** follow patients eligible for the investigation cohort.

**An investigation cohort of at least 262 patients** can be mobilised via these centres.

| | *1* | *2* | *3 4 5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* | *20* | *21* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **FBN1 mutation** | **Antwerp** | **Ghent** | **Leiden/ Nijmegen/ Gronigen** | **Amsterdam** | **Paris** | **London** | **Berlin** | **Munich** | **Hamburg** | **Sheffield** | **Zurich** | **Milan** | **Pavia** | **Bologna** | **Barcelona** | **Rome** | **Umea** | ***Ottawa*** | ***Baltimore*** | **TOTAL** |
| **#3 p.Ala882Val; c.2645C>T – exon 21** | 0 | 4 | 1 | 0 | 53 | 6 | 0 | 0 | 1 | 3 | 3 | | 1 | 3 | | | | | *4* | 79 |
| **#7 p.Ile2585Thr; c.7754T>C – exon 62** | 8 | 13 | 20 | 2 | 93 | 12 | 10 | 0 | 2 | 1 | | 3 | 2 | | 3 | 1 | 4 | *6* | *3* | 183 |
| **Number of patients** | **8** | **17** | **21** | **2** | **146** | **18** | **10** | **0** | **3** | **4** | **3** | **3** | **3** | **3** | **3** | **1** | **4** | ***6*** | ***7*** | **262** |
| | *3%* | *6%* | *8%* | *1%* | *56%* | *7%* | *4%* | *0%* | *1%* | *2%* | *1%* | *1%* | *1%* | *1%* | *1%* | *0%* | *2%* | *2%* | *3%* | *100%* |
| **Distance from UZA (km)** | 0 | 60 | 138 | 180 | 348 | 378 | 722 | 777 | 564 | 654 | 693 | 947 | 984 | 1161 | 1376 | 1519 | 2166 | *5655* | *6145* | |

It cannot be guaranteed at this stage that it will be possible to carry out grouped collections followed by grouped shipments. At this stage, the cautious approach would be **to plan for 262 individual shipments**.

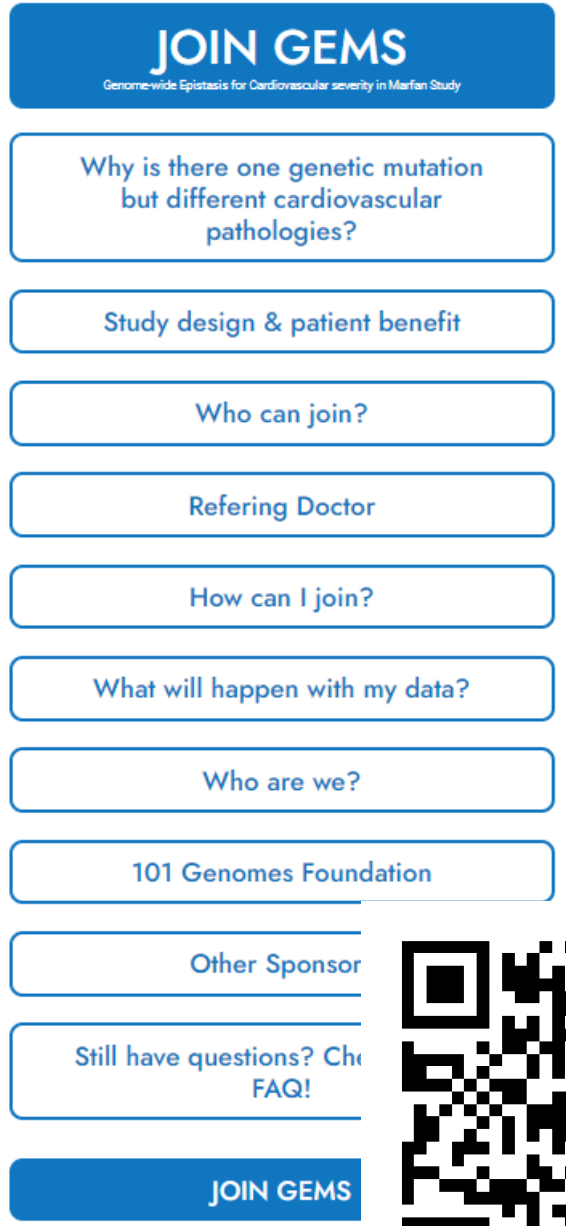
Azure

DocuSign

its me

# 101 GEMS App

Web application for consent collection, consent management and phenotypic data collection




**https://www.101gems.be/**

# Flow

## GEMS2Patient


101 GEMS App

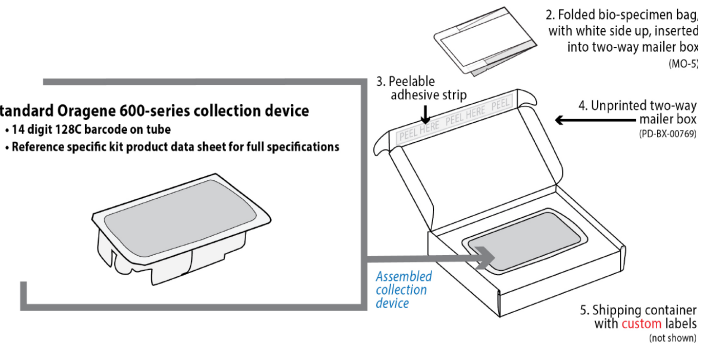
bpost

bpost

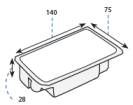
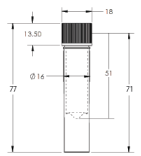
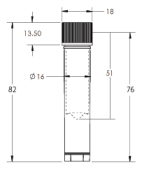

UZ GENT

101 Genomic Cloud

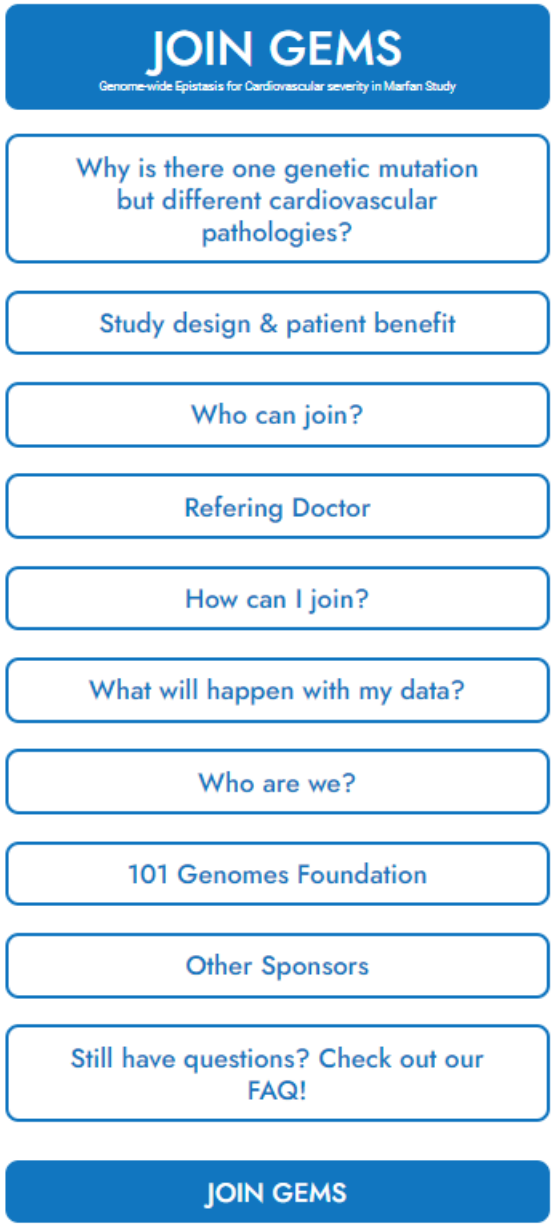
**Accessory pack (ACP-055) components:**



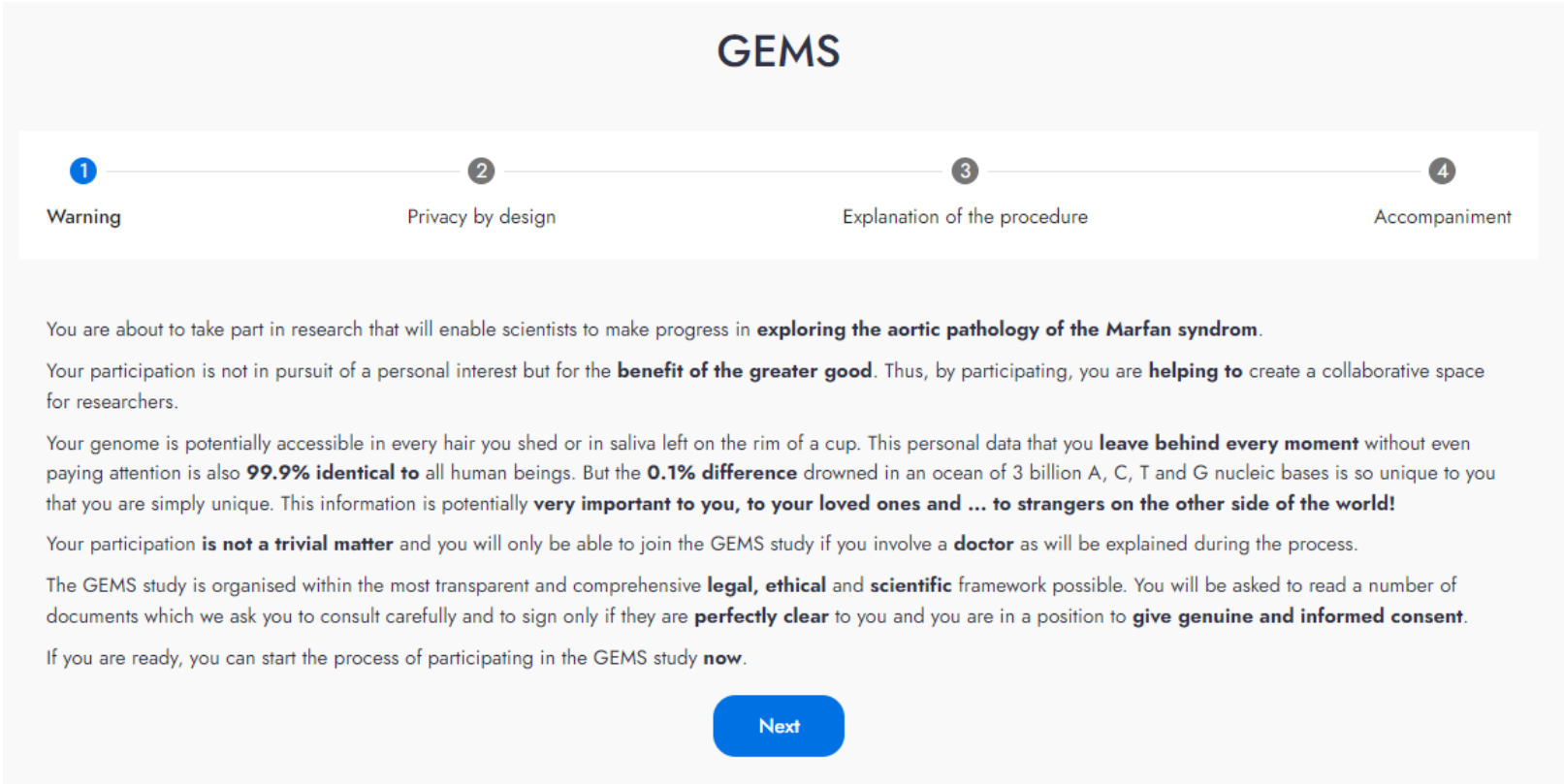

DNAgenotek **Oragene® 600 series product weight and dimensions**

| | Catalogue numbers | Saliva volume | Pre-collection: Package dimensions and contents — WEIGHT 34-38g† — Clamshell (mm) | Components | Collector | Post-collection: Total sample volume†† | Tube dimensions (mm) |
|---|---|---|---|---|---|---|---|
| Without 2D bottom barcode | OG(X)-600 | 2 mL |  |  |  | 4 mL |  |
| | OG(X)-675 | .75 mL via sponge | | | | 1.5 mL | |
| | OG(X)-610 | 1 mL | | | | 2 mL | |
| | ON-600 | .5 mL | |  | | | |
| With 2D bottom barcode | OG(X)-600.S2P | 2 mL | | | OR | 4 mL |  |
| | OG(X)-675.S2P | .75 mL via sponge | |  |  | 1.5 mL | |
| | OG(X)-610.S2P | 1 mL | | | | 2 mL | |
| | ON-600.S2P | .5 mL | | | | | |

† Weight is inclusive of all product configurations within referenced catalogue numbers.
†† Total sample volume includes saliva and Oragene stabilization solution. May vary based on volume of saliva collected.

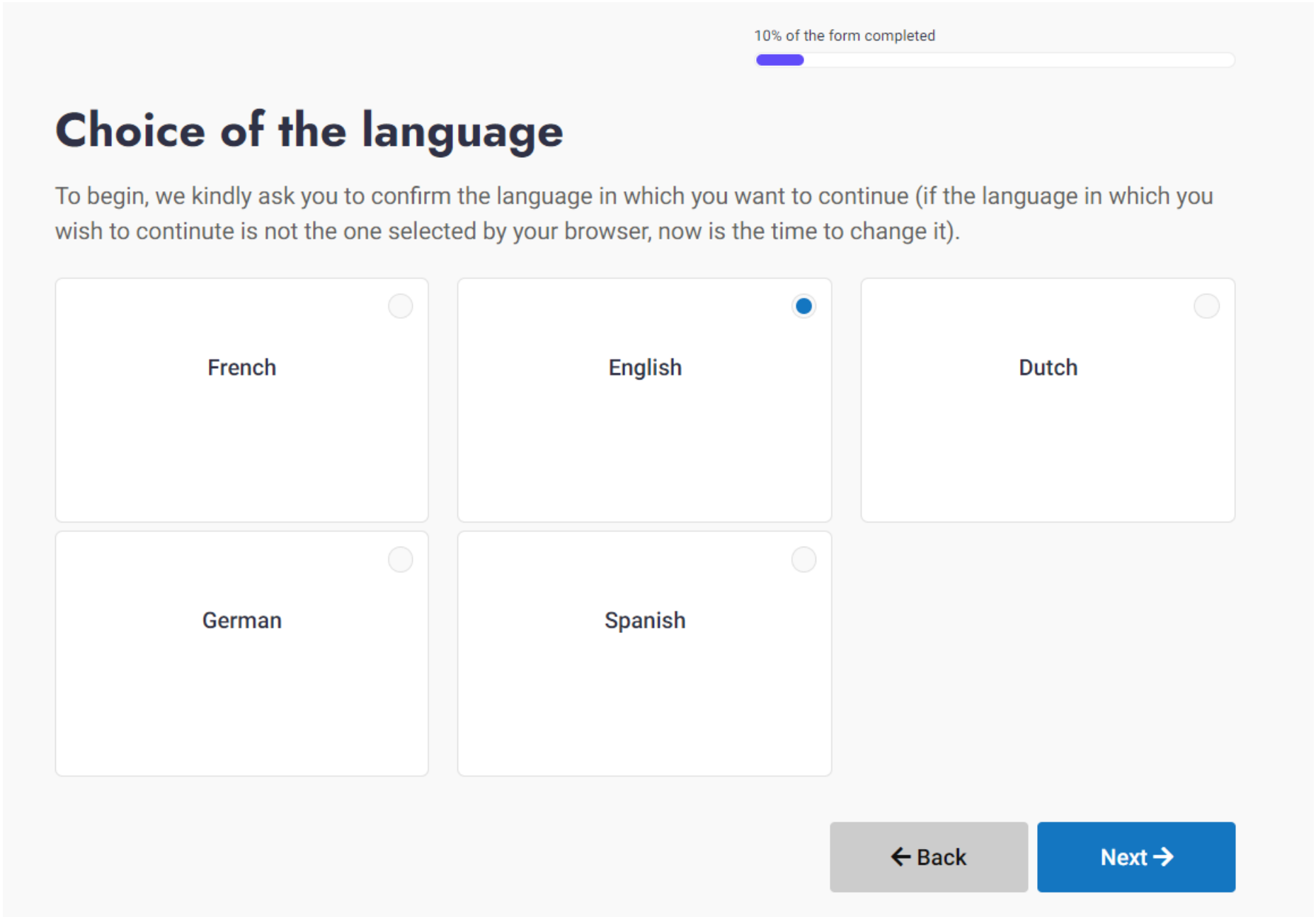



# https://www.101gems.be/




Azure DocuSign itsme

# Consent


10% of the form completed
Choice of the language
To begin, we kindly ask you to confirm the language in which you want to continue (if the language in which you wish to continute is not the one selected by your browser, now is the time to change it).
French
English
Dutch
German
Spanish
← Back
Next →

10% of the form completed

# Personal capacity or as legal representative

Then we ask you to precise if you are filling this form in your personal capacity or as the legal representative of someone else.

- (●) I am completing the present form in my personal capacity
- ( ) I am completing the present form as the legal representative of an adult with a legal incapacity
- ( ) I am completing the present form as the legal representative of a child over the age of 12
- ( ) I am completing the present form as the legal representative of a child under the age of 12

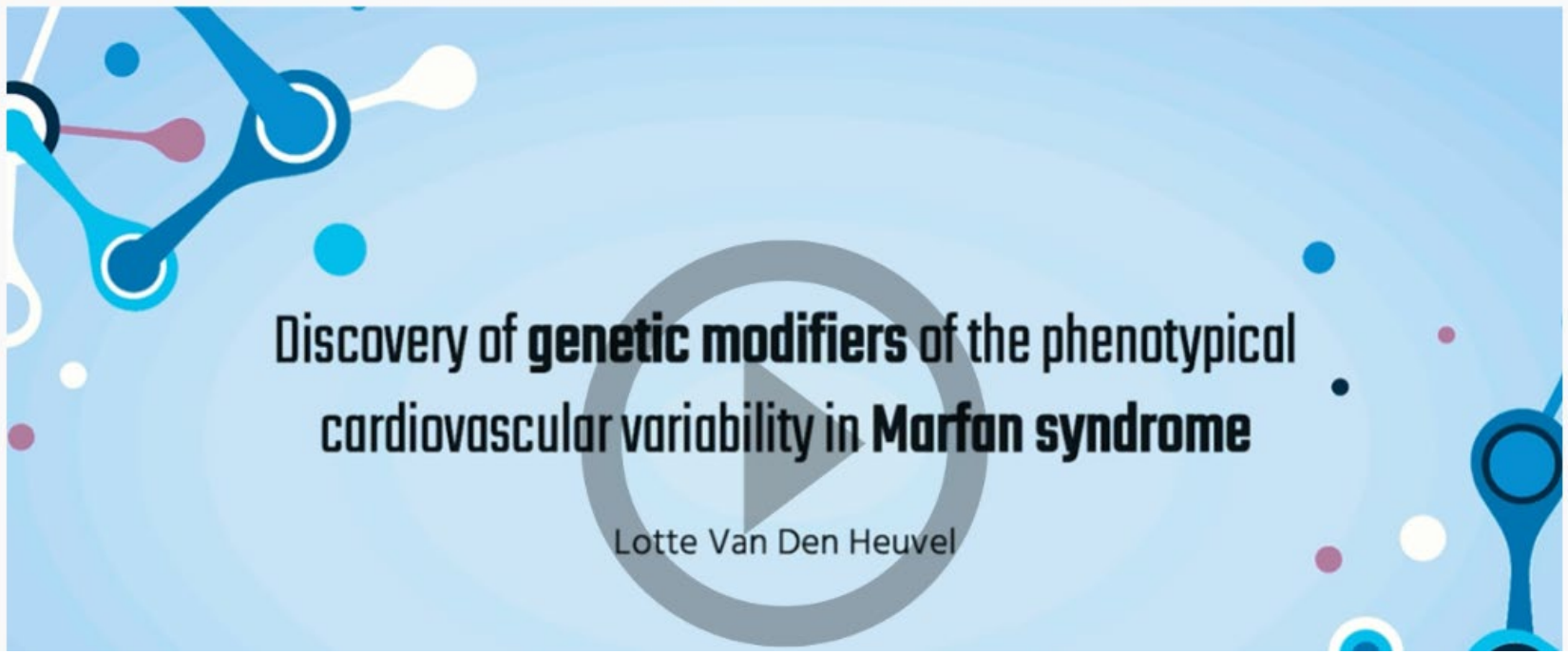
← Back  Next →

20% of the form completed

# Video and documentation

Before joining the "***G**enome-wide study **E**pistasis for cardiovascular severity in **M**arfan **S**tudy (GEMS)*" which studies the interactions between genes in the entire genome in order to better understand the severity of cardiovascular damage in the Marfan syndrome, we invite you to:

1. watch the GEMS presentation **video**;
2. read the GEMS study **patient information sheet and informed consent form**;
3. read the **privacy policy** of the 101 Genomes Foundation **accessible via this link**.



30% of the form completed

# Verification

In order to verify that **your consent is informed and genuine**, you must now **correctly answer the following five questions** to allow you to continue with the process.

If you do not answer correctly, you will be asked to repeat the process until you have answered all five questions correctly.

For your information, the questions are randomly generated and **the number of attempts is unlimited**.

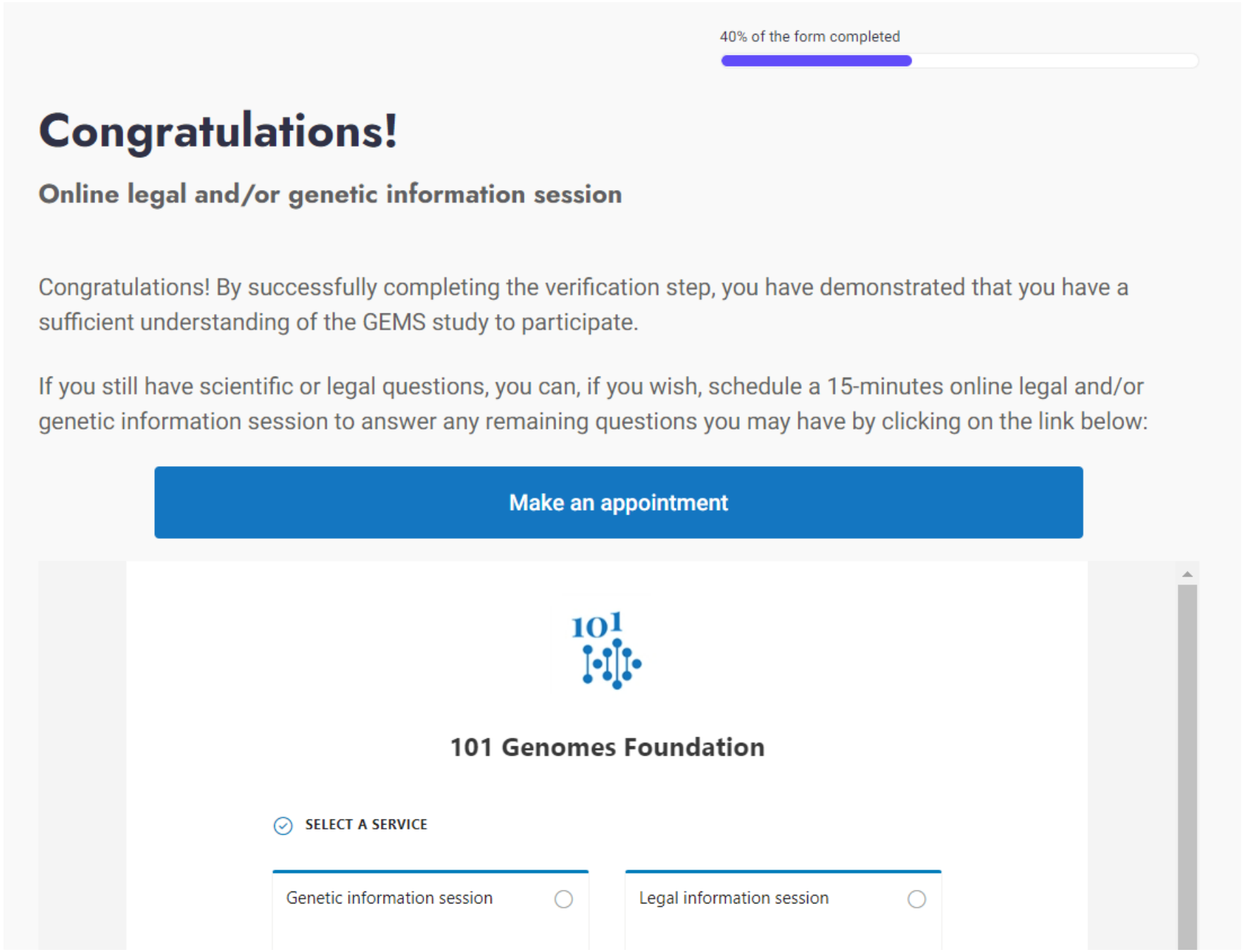
PS: All the answers to the questions can be found on **the home and warning pages**.

---

How can I find out the results of this GEMS study?

- ○ I will always be contacted individually about my personal results
- ○ I will be informed through the F101G website, the general public and Marfan patient associations
- ○ GEMS research results will never be made public

What is the main objective of the research proposed in the GEMS study with respect to Marfan syndrome?


40% of the form completed
Congratulations!
Online legal and/or genetic information session
Congratulations! By successfully completing the verification step, you have demonstrated that you have a sufficient understanding of the GEMS study to participate.
If you still have scientific or legal questions, you can, if you wish, schedule a 15-minutes online legal and/or genetic information session to answer any remaining questions you may have by clicking on the link below:
Make an appointment
101
101 Genomes Foundation
SELECT A SERVICE
Genetic information session
Legal information session

50% of the form completed

# GEMS consent

INFORMED CONSENT: Investigation of genome-wide gene interactions to better understand cardiovascular severity in Marfan syndrome to pave the way for individualized treatment protocols.

- I confirm that I am thoroughly informed about this study and received a copy of the “patient information sheet and informed consent”. ☑
- I read these documents, understood this information and had sufficient time to ask questions. My research physician has explained the study with regards to the conditions, duration, the effect and risks. ☑
- I understood that my participation in this study can be stopped any time after informing my research physician, without any influence for further medical care. ☑
- I give permission to the initiator of this study, Prof. Dr. Bart Loeys and associated organisations (after pseudonymisation) to have access to my medical records. My medical records will be handled strictly confidential and used in the framework of this study. ☑
- I give permission to assembly, process and use my medical records as described by the information sheet for the patient. I also give permission to use and process this data in other European countrieswithin the international context of this study. ☑
- I voluntarily give my consent to participate in this research and all associated examinations. I am willing to give further information about my medical history, use of medications, and cooperation in other studies. ☑
- I give permission to involve my general practitioner, specialists or other caretakers involved in my medical care. If necessary they can be informed about my participation in this study. ☑

60% of the form completed

# Signature

We now invite you to formalise your consent, sign all legal documents and provide us with the information necessary to participate in the GEMS study using the "DocuSign" interface which will allow you to be officially identified and authenticate your signature.

You will be redirected to the "DocuSign" interface and will then return to the form.

## Personal information

First name

Romain

Family name

Alderweireldt

Phone number

+32475859824

Day of birth

03/09/2015

Gender

Other

## Home address

DocuSign®

:/Signing/?insession=1&ti=88a1d37f5aca4d49b3313d0e7ae9b3de

FINISH

START

DocuSign Envelope ID: 5A2E5F0E-8D68-4825-A632-C0E9F23818E7





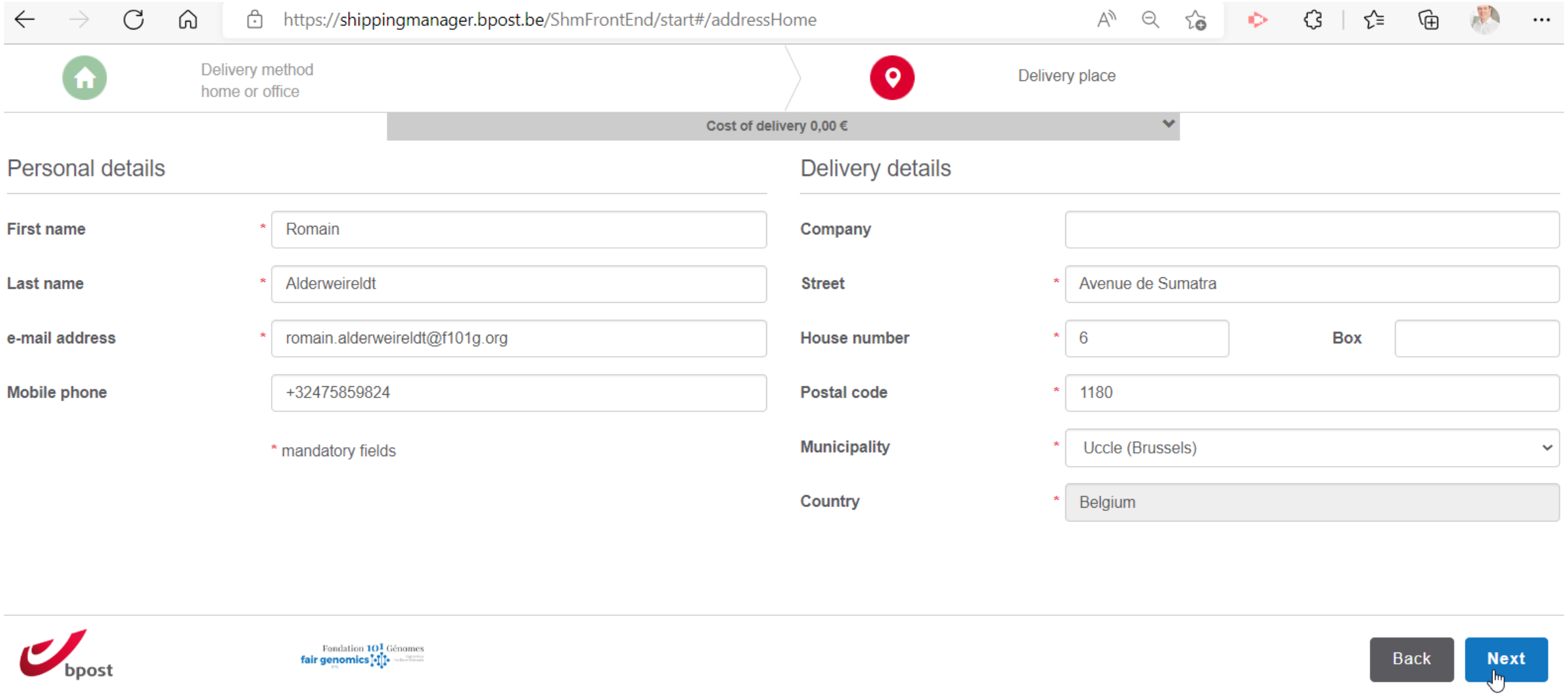
## Patient information sheet / informed consent (English)

**Title of the study:** Genome-wide Epistasis for cardiovascular severity in Marfan Study (GEMS) to pave the road to individualized treatment protocols

**Initiator of the study:** Center for Medical Genetics, Antwerp University Hospital, PrinsBoudewijnlaan 43/6, 2650 Antwerp-Edegem-Belgium

**Ethical committee:** EC, Antwerp University Hospital

**Research physician:** Prof. Dr. Bart Loeys, Center for Medical Genetics, Antwerp University Hospital, PrinsBoudewijnlaan 43/6, 2650 Antwerp-Edegem Belgium. Tel: ++ 32-3-275.97.74


https://shippingmanager.bpost.be/ShmFrontEnd/start#/addressHome
Delivery method
home or office
Delivery place
Cost of delivery 0,00 €
Personal details
First name * Romain
Last name * Alderweireldt
e-mail address * romain.alderweireldt@f101g.org
Mobile phone +32475859824
* mandatory fields
Delivery details
Company
Street * Avenue de Sumatra
House number * 6
Box
Postal code * 1180
Municipality * Uccle (Brussels)
Country * Belgium
bpost
Fondation 101 Génomes
fair genomics
Back
Next

60% of the form completed

# Signature

Thank you!

We confirm that you have signed the consent form to join the GEMS study.

Your signed form is now available for download via your profile management interface and you will receive a copy when it has also been countersigned by the researcher in charge of the GEMS study.

Within a few days, you will receive a kit containing all the necessary material and instructions for the collection of a saliva sample and its prepaid shipment to the analysis laboratory.

← Back  Next →

70% of the form completed

# FBN1 mutation

Could you please inform us of the FBN1 mutation that was communicated to you at the time of your diagnosis which makes you eligible to participate in the GEMS study? This information will allow us to redirect your data in the investigation cohort or in the control cohort?

- I am a carrier of the c.7754T>C (c.DNA reference) or p.Ile2585Thr (protein reference) mutation on the FBN1 gene
- I am a carrier of the c.2645C>T (c.DNA reference) or p.Ala882Val (protein reference) mutation on the FBN1 gene
- I have another mutation
- I don't know the mutation that caused my Marfan syndrome diagnosis.

← Back  Next →

90% of the form completed

# Invitation to donate

Your participation in the GEMS study costs nearly 1000 euros to the 101 Genomes Foundation.

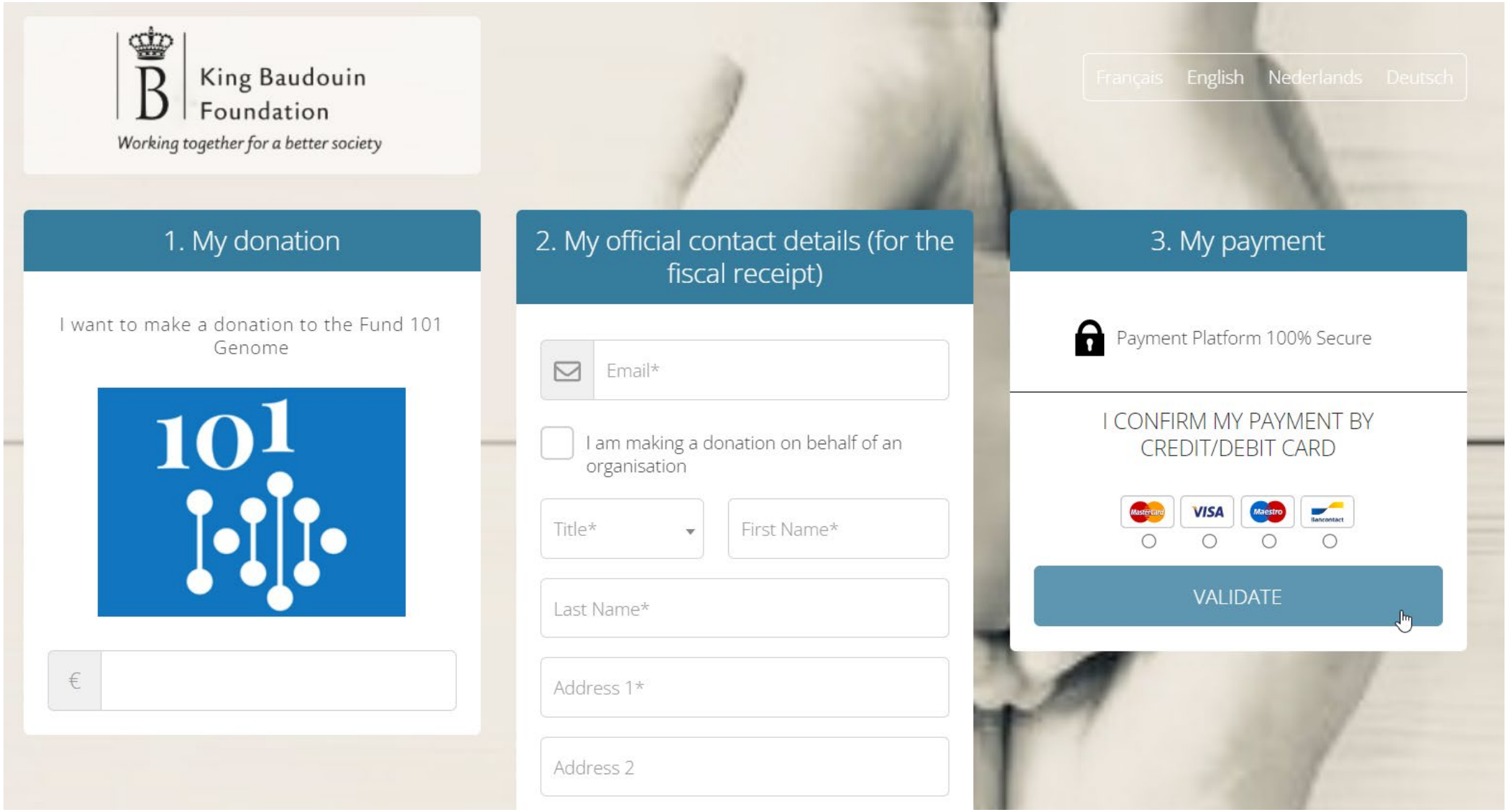
If you wish, but it is absolutely not obligatory, you can now proceed to a **tax-deductible donation** (anywhere in Europe over 40 euros) which will cover all or part of this cost and support the work of the 101 Genomes Foundation.

**Tax-deductible donations can be made online** via the secure module made available to us by the King Baudouin Foundation by clicking below:

Donate

Alternatively, donations can be made to the **King Baudouin Foundation** for the benefit of the 101 Genomes Fund to IBAN account: **BE10 0000 0000 0404** | BIC: BPOTBEB1 with Structured Communication: ***017/1730/00036***.

← Back  Next →


King Baudouin Foundation
Working together for a better society
Français English Nederlands Deutsch
1. My donation
I want to make a donation to the Fund 101 Genome
101
€
2. My official contact details (for the fiscal receipt)
Email*
I am making a donation on behalf of an organisation
Title*
First Name*
Last Name*
Address 1*
Address 2
3. My payment
Payment Platform 100% Secure
I CONFIRM MY PAYMENT BY CREDIT/DEBIT CARD
VALIDATE

100% of the form completed

# Thank you for joining GEMS!

Dear GEMS participant,

We confirm that your consent has been registered and that a saliva sampling kit will be sent to the address you have provided.

The 101 Genomes Foundation and Professors Bart Loeys and Paul Coucke thank you for your trust. Your participation will help to advance the understanding of Marfan syndrome. A better understanding of Marfan syndrome and how certain genes interact with each other to prevent or aggravate the cardiovascular damage caused by this disease opens the way to better diagnosis and new therapeutic horizons.

On behalf of all those affected by Marfan syndrome and their families: THANK YOU!

**Manage your profile**

All the information you have provided to us and the consent documents you have signed are now available via your online profile management portal at: **https://www.101gems.be/profile**.

Through this portal, you will be able to update and complete the information you have provided at any time and to see the research and publications that have been produced thanks to your participation.

100% of the form completed

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# Profile management

# Profile Management

## Privacy Management Dashboard

Info | Referring doctor | Consent | Health Data | Impact | Kit | GDPR

## Personal information

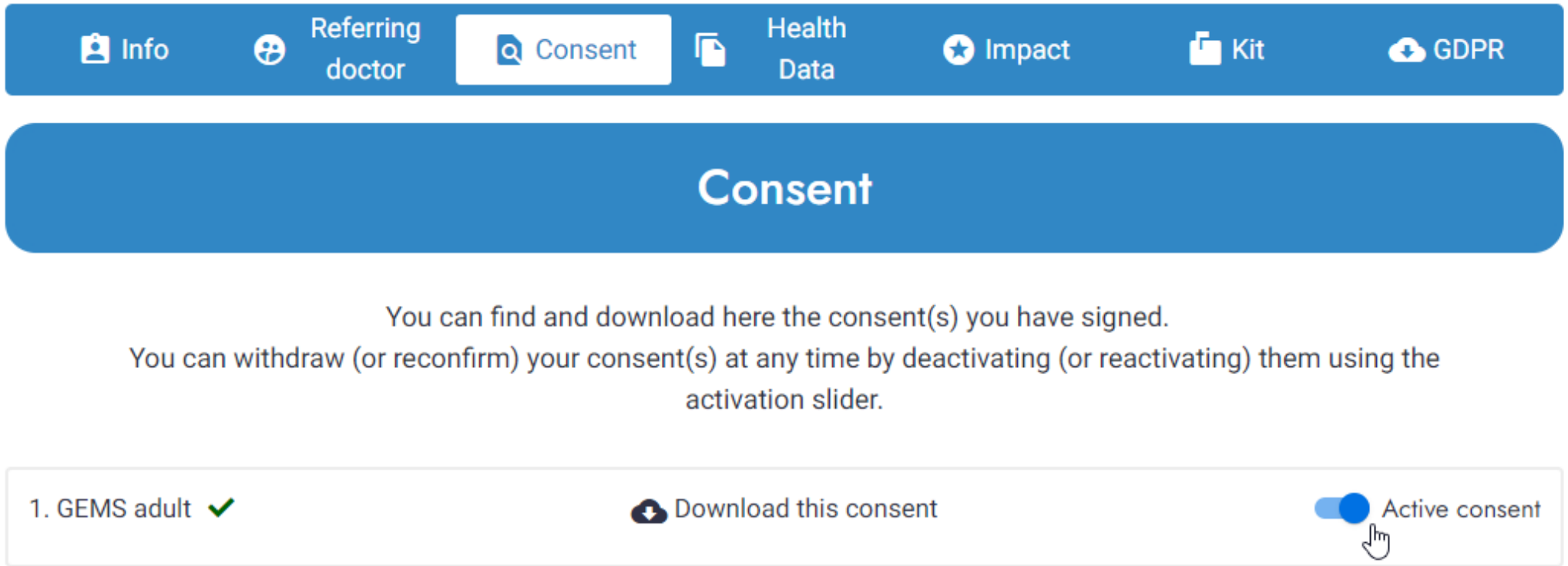
On this page you can find the personal information you have shared with us.
You can update this information at any time here.

# Profile Management

## Privacy Management Dashboard

# Profile Management

## Privacy Management Dashboard



# Profile Management

## Privacy Management Dashboard

Info | Referring doctor | Consent | Health Data | Impact | Kit | GDPR

## Research groups

You can find here the names of the research groups that have been granted access to data collected by the 101 Genomes Foundation.

## Publications

You can find here the references of scientific publications based on data collected by the 101 Genomes Foundation.

# Profile Management

## Privacy Management Dashboard

Info | Referring doctor | Consent | Health Data | Impact | Kit | GDPR

### Kit registration

On this page you are asked to provide the date when you used the kit and to enter the barcode number of your saliva collection kit (which appears on the kit itself and on the accompanying letter).

Could you please indicate here the date on which you used the saliva sample collection kit? Please note that without this date, the sample cannot be sequenced.

*dd/mm/yyyy*

Could you please indicate here the barcode number of your saliva collection kit (which appears on the kit itself and on the accompanying letter)?

*12345678901234*


Save

# Profile Management

## Privacy Management Dashboard


## Rights under the GDPR

Via the "Manage your profile - Privacy management dashboard" portal you are able to exercise all the rights granted to you by the GDPR.

You can exercise:
- your right to information, in particular, via the "Impact" page;
- your rights of access and rectification via the "Info", "Referring doctor" and "Health data" pages;
- your rights to withdraw consent, erasure, opposition to processing and restriction of processing via the "Consent" page;
- your right to the portability of personal data by downloading all the personal data we have collected via the link below "Download my data".

Download my data

# Phenotypic data (health data)

# Profile Management

https://www.101gems.be/pheno

## Privacy Management Dashboard

Info | Referring doctor | Consent | Health Data | Impact | Kit | GDPR

## Health data

On this page you can find the health data you have shared with us.
You can complete and update this information at any time via the link below to the PHENO boxes.

PHENO Boxes (update)

## PHENO Boxes

Via the different "boxes" below you can choose to communicate health data that are very important for the GEMS project: these data will help to "decipher" the alphabet of the genome and shed light on the interaction between genes.

You can communicate this information in stages and come back regularly to update it. Each completed box changes colour and appears in green.

- Information
- Family
- Ethnicity
- Aorta aneurysma
- Aorta medication
- Aorta surgery
- Aorta dissection
- Confounding factors
- Hypertension

## Aorta surgery

Have you ever had surgery on the aorta (root and/or valve)?

Yes | Non

Can you tell us what type of aortic surgery you had?

Bentall | David | PEARS | Supra-coronair | I don't know

Can you tell us in millimeters what the largest measured diameter of your aorta was before surgery?

Largest diameter in millimeters

# items ()

# Short list

## GEMS only

**Contact information center of the patient:**

Center: _____

Physician: _____

E-mail: _____

Telephone number: _____

**Patient information:**

Mutation: *FBN1*p.Ile2585Thr; c.7754T>C / p.Ala882Val; c.2645C>T

Patient ID: GEMS-_____

Family history of MFS: Yes / No, number of affected family members: _____

Related to patient ID: _____ Relationship: _____

Ethnicity: Caucasian / Afro-American / Hispanic / Asian / other:_____

Year of birth: _____ Sex: M / F/ X

Weight: _____kg (year: _____)Height: _____cm (year: _____) Armspan: _____cm (year: _____)

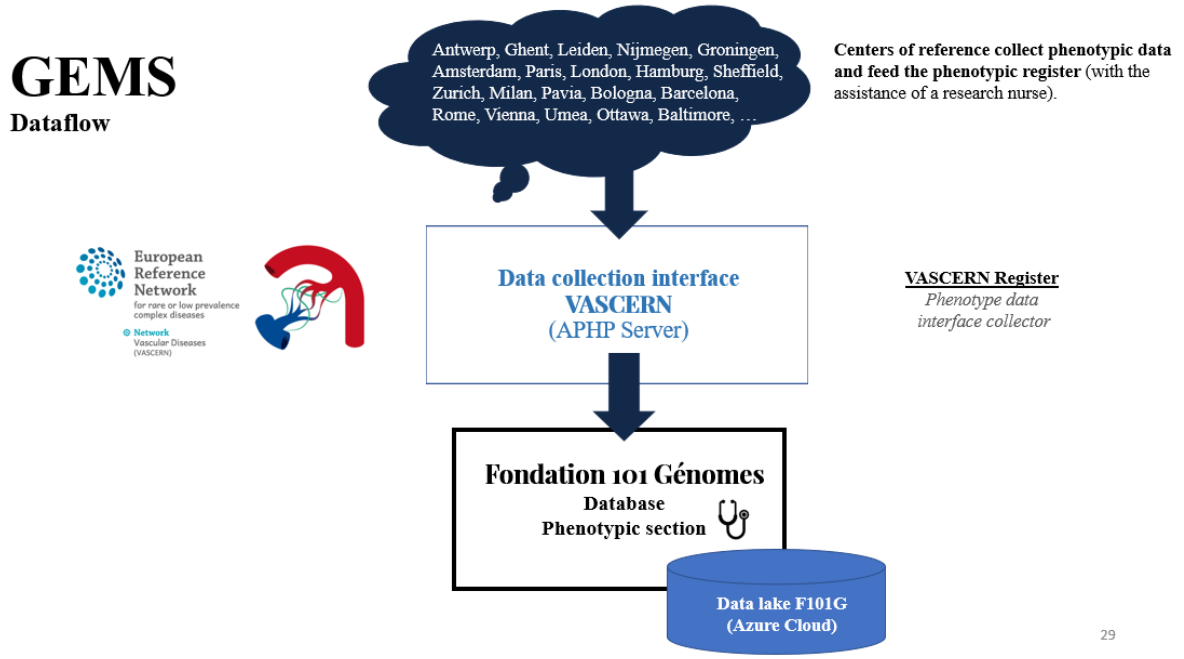
Epiphysiodesis: No / Yes; year _____ Last height before surgery: _____cm
Hormone therapy: No/ Yes; years Last height before hormone therapy:____cm (year:_____)
Wrist sign: Yes/ No / unknown Thumb sign: Yes/No / unknown
Scoliosis: Yes/ No /unknown; if yes; Cobb's angle: _____° (year:_____)
Spine surgery:No / Yes; year _____ Cobb's angle before surgery:_____°
Pectus deformity: No / pectus carinatum/pectus excavatum / unknown / surgery (year:_____)
Pes Planus: Yes / No / unknown Skin striae: Yes / No / unknown
In case of aortic dissection; ☐Type Ayear: _____ ☐Type B year: _____
Largest aortic diameter before dissection: _____ mm; level:_____
In case of aortic surgery; year: _____ ☐ Bentall ☐ Valve sparing☐ Supra-coronary ☐ PEARS
Last aortic diameter before surgery: _____ mm; level:_____
Aortic aneurysm:☐Sinus ☐ Ascending ☐ Arch ☐ Descending thoracic ☐ Abdominal
First imaging study **ever**; year: _____
Diameters: aorta sinus: _____ mm aorta ascendens: _____ mm
Last imaging study**available;** year: _____
Diameters: aorta sinus: _____ mm aorta ascendens: _____ mm

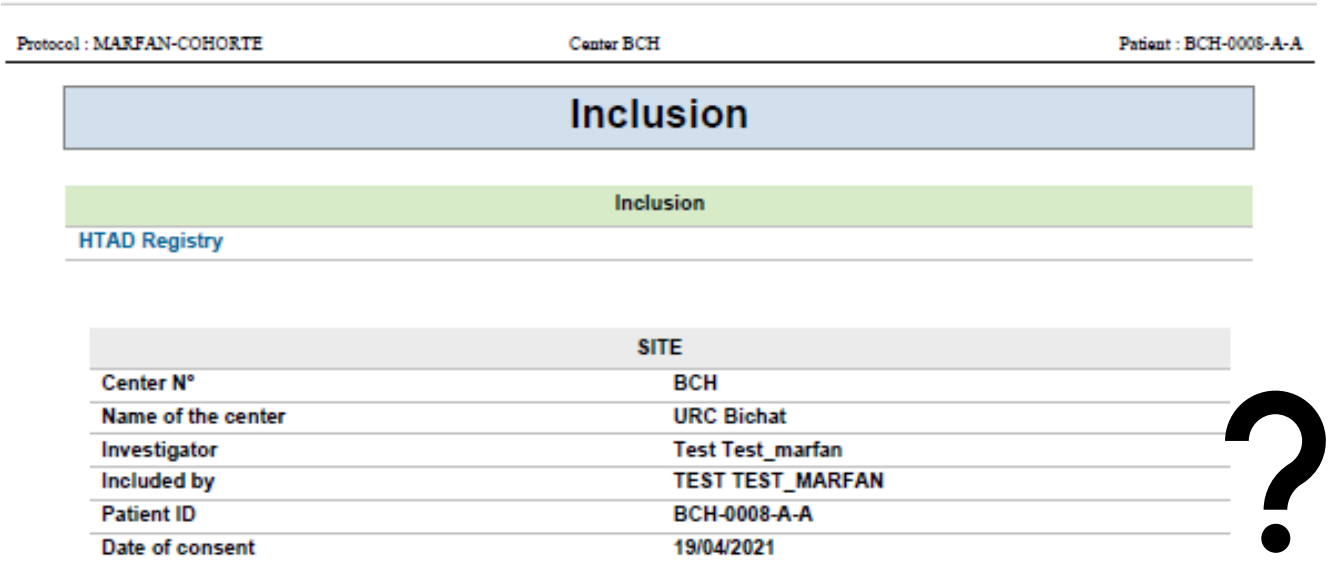
SurgicalHistory :
☐ Aortic Valve: ☐ Mechanical ☐Bioprosthetic ☐Plasty (repair)
☐ Mitral Valve: ☐ Mechanical ☐Bioprosthetic ☐Plasty (repair)
☐ Descending Aorta/ ☐aortic arch ☐ Endoprosthesis ☐ Open surgery

Aortic medication: Yes / No ☐beta-blocker ☐sartan☐other
If yes, which one: _____ started since: year:_____
Hypertension: Yes / No, if yes hypertension: in history or currently
If woman: number of pregnancies 0 / 1 / 2 / 3 / 4 (years of delivery:_____)

# Long process
## with HTAD VASCERN

- 20161222 MAC Phenotype data collection template ORIGINAL
- 20180101 LOEYS Formulaire
- 20180122 NECKER BICHAT Marfan data file Paris 2018 v0
- 20180131 20161222 MAC Phenotype data collection template
- 20180219 P101GM Formulaire collecte données phénotypiques vRGA
- 20180228 LOEYS Formulaire Anvers Final MFS checklist
- 20180404 DE BACKER Clin data file_Ghent
- 20180608 RGA LUDI Formulaires collectes données phénotypiques
- 20180615 DE BACKER JONDEAU Formulaire collecte données phénotypiques_101 genom...
- 20190208 F101G P101GM Formulaire collecte données phénotypiques_101 genomes
- 20190208 UZA Formulaire
- 20191006 JDB Formulaire collecte données phénotypiques_101 genomes
- 20191013 JDB Formulaire collecte données phénotypiques_101 genomes
- 20210506 RGA T154559_MARFAN-COHORTE_BCH-0008-A-A
- 20211130 GJ HTAD_Liste_variables_ revue gj



# Difficult to measure

## Objectivation: Aorta Automatic Measurements AORAM

cytomine

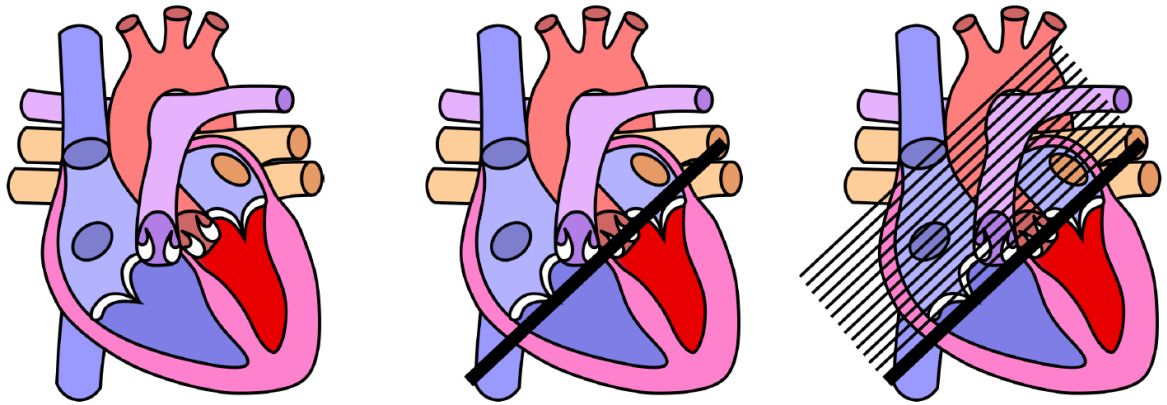
COLLABORATIVE BIOMEDICAL IMAGE ANALYSIS

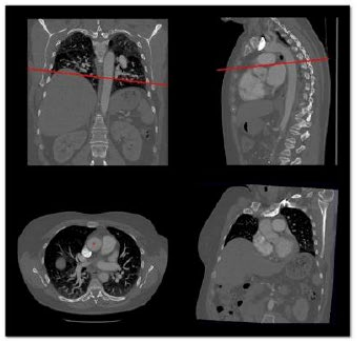
FARI AI FOR THE COMMON GOOD INSTITUTE BRUSSELS

- **Alpha 1** - manual tool to explore medical images, annotate them and train algorithms
- **Alpha 2** - expand Alpha 1 for automatic detection of the aortic valve reference plane
- **Alpha 3** - logical workflow managing Alpha 1 and Alpha 2

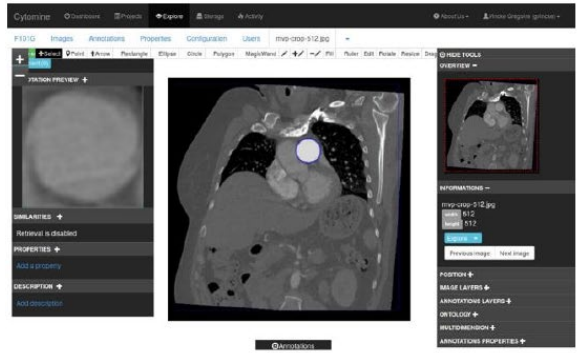
### Challenge

**Extraction of slices throughout the 10 first centimeters of the aorta and AI computation of metrics**





**Osimis : CT/MRI slicer**

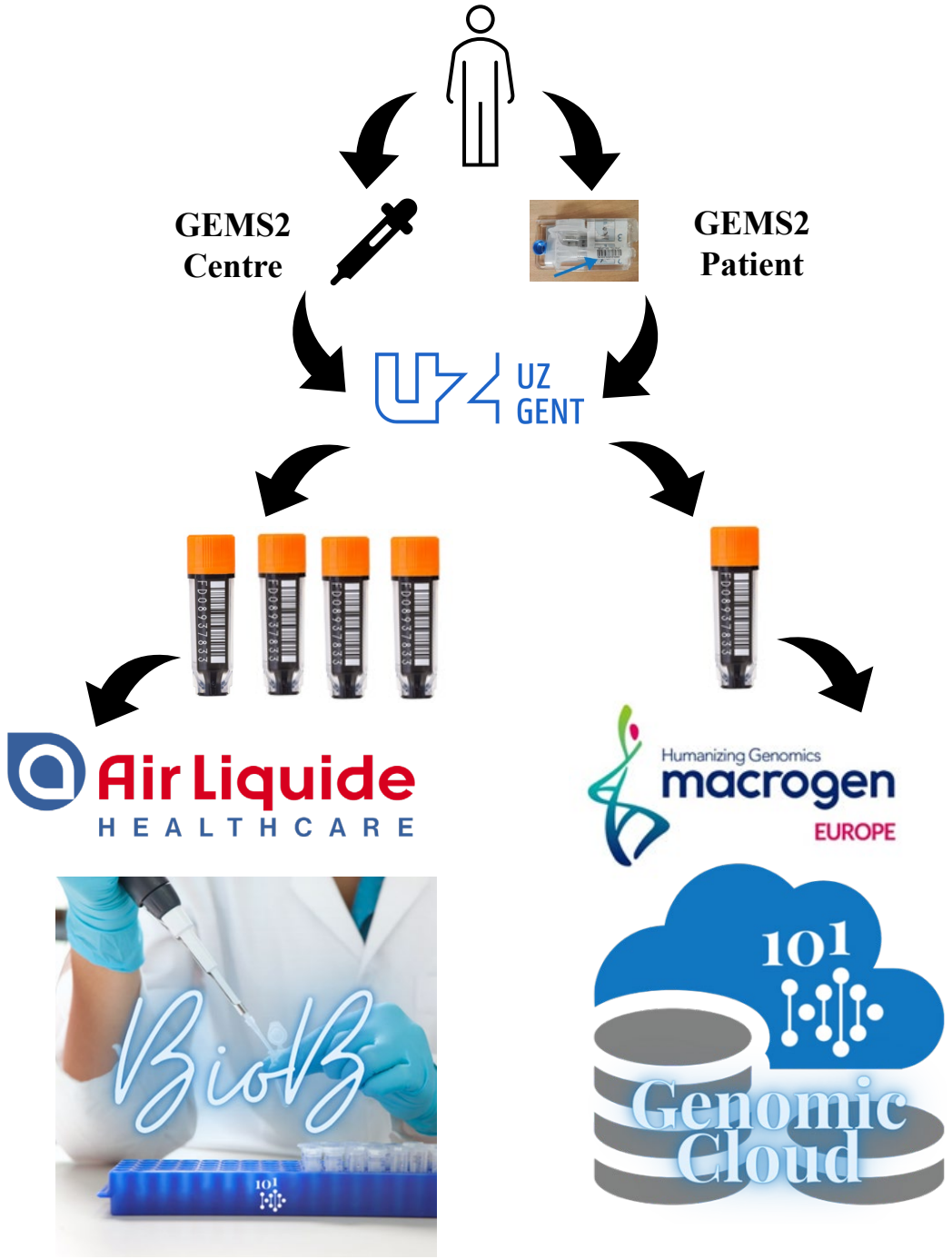


**Cytomine : annotation and AI**

# Back to GEMS

# How can we make the GEMS search for protective genes a reality?

# By creating a Biobank and a Bio-biobank!




The samples are collected in the laboratory in Ghent.

There, **DNA is extracted** and distributed for each patient in 5 DNA storage tubes (screw caps).

**One DNA** storage tube is sent to MacroGen for sequencing and

**Four DNA** storage tubes are stored in the BioBank.


# Biologic storage

# CryopAL Biobanque Solutions

## Convention

| Catégories | Recherche portant sur un médicament | Recherche impliquant la personne humaine (RIPH) | | |
|---|---|---|---|---|
| Titre | Recherche interventionnelle portant sur un médicament | Recherche interventionnelle ne portant pas sur un médicament | Recherche interventionnelle à risques et contraintes minimes | Recherche non interventionnelle |
| Abbréviation | EC médicament | RIPH1 | RIPH2 | RIPH3 |
| Exemple | | • Collecte de sang hors conditions de l'arrêté du 12/04/2018 | • Prélèvement de sang effectué spécifiquement pour la recherche hors contexte de soin<br>• Collecte dans les conditions de l'arrêté du 12/04/2018 | • Prélèvement supplémentaire pour la recherche réalisé dans le cadre du soin |
| Autorisations recherche | Autorisation UE<br>Portail européen CPP | Autorisation ANSM<br>Avis favorable CPP | Enregistrement ANSM<br>Avis favorable CPP | |

**Entre les soussignés :**

La société CryopAL Biobanque Solutions, une société anonyme à conseil d'administration dont le numéro de SIRET est le 529 218 638 00029, le numéro de TVA intracommunautaire est le FR 84 529 218 638 et dont le siège social est situé Parc Gustave Eiffel, 8 avenue Gutenberg, 77600 Bussy Saint Georges

représentée aux fins des présentes par Monsieur Yves Patin, Directeur Général

Ci-après dénommée **« CryopAL Biobanque Solutions »**

**D'une part,**

**Et**

La Fondation 101 Génomes (F101G), fondation privée de droit belge, inscrite à la banque carrefour belge des entreprises sous le numéro BE0684609172 et dont numéro de TVA intracommunautaire est le BE 684 609 172 et dont le siège social est situé avenue de Sumatra, 6 à 1180 Bruxelles, Belgique.

représenté aux fins des présentes par Romain Alderweireldt, administrateur de la F101G.

Ci-après dénommé le **« Déposant »**

**D'autre part,**

CryopAL Biobanque Solutions et le Déposant étant individuellement désignés par la « Partie » et collectivement par les « Parties ».

# ERASME-ULB ethic committee

## 5 April 2022: 'Avis favorable'

- **Comité·d'Ethique·Hospitalo-Facultaire·Erasme-ULB**¶

¶

https://www.erasme.ulb.ac.be/fr/ethique¶

¶

¶

Pour·un·contact·avec·le·secrétariat·du·CE¶

**tél**°:·32·2·555·3707¶

**e-mail**°:·comite.ethique@erasme.ulb.ac.be¶

¶

Pour·la·soumission··de·votre·dossier·au·format·papier¶

A·l'attention·de·Mme·Hélène·François¶
Comité·d'Ethique·Erasme-ULB·(local·0W7010,·route·843)↵
Route·de·Lennik·808¶
1070·Bruxelles¤

¶

Pour·la·soumission·de·votre·dossier·au·format·électronique¶

**e-mail**°:·comite.ethique@erasme.ulb.ac.be¶

¶

¶

**Demande·d'avis·du·Comité·d'Ethique·↵**
**constitution·/·renouvellement·d'agrément¶**
**Etablissement·de·Matériel·Corporel·Humain·(MCH)¶**

¤

¶

Cliniques universitaires de Bruxelles
Route de Lennik 808
B-1070 Bruxelles
T +32 (0)2 555 31 11
M contact@erasme.ulb.ac.be
S www.erasme.ulb.ac.be

Hôpital Erasme — ULB

Dr VERBOOGEN Michel
Médecin, Neuropsychiatre,
Président du Conseil d'administration
de la Fondation 101 Génomes
Rue Cambron, 31
7500 Tournai

Bruxelles, le 05/04/2022

Comité d'Ethique
hospitalo-facultaire
Erasme - ULB
(021 / 406)

Secrétariat
T 02 555 37 07
02 555 37 11
F 02 555 46 20
M comite.ethique@erasme.ulb.ac.be
www.erasme.ulb.ac.be/ethique

Cher VERBOOGEN Michel,

Dans le cadre de sa mission légale définie à l'article 7, §1er, alinéa 3, de la loi du 19 décembre 2008 relative à l'obtention et à l'utilisation de matériel corporel humain destiné à des applications médicales humaines ou à des fins de recherche scientifique, le Comité d'Ethique hospitalo-facultaire Erasme-ULB a pris connaissance du dossier de soumission de la biobanque de MCH « Biobanque de matériel corporel humain de la Fondation 101 Génomes » (Ref. B2022/001).

Le dossier évalué comprend les pièces suivantes :

- Cover Letter, dated March 13, 2022
- Demande d'avis du Comité d'Ethique, dated March 13, 2022
- Annexe : lien : 20220313 F101G Biobanque

**Le Comité octroie, en date du 05/04/2022, un avis favorable par rapport aux activités et objectifs, tels que décrits dans le dossier de soumission**

Nous vous prions d'agréer, Cher VERBOOGEN Michel, l'expression de nos meilleurs sentiments.

Pr J.M. BOEYNAEMS
Président

# AFMPS

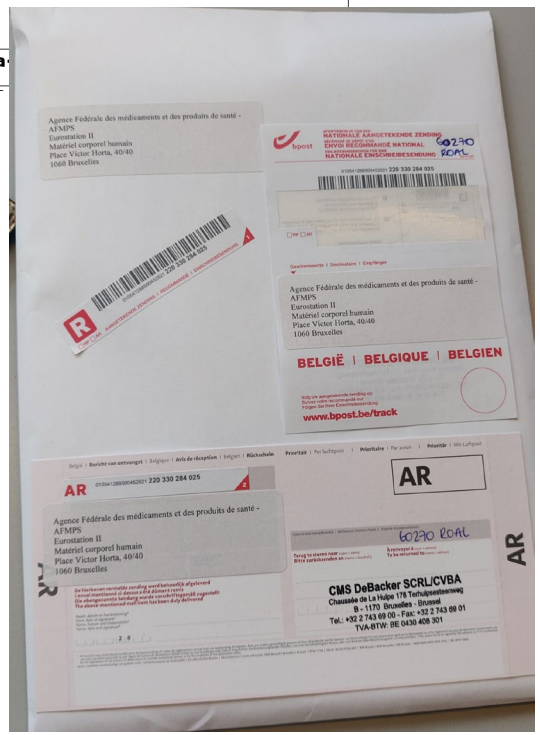
## Notification (18 May 2022) & Confirmation (9 June 2022)

**FORMULAIRE·DE·NOTIFICATION·DE·LA·BIOBANQUE¶**

Ce·document·est·le·formulaire·de·demande·de·notification·tel·que·mentionné·dans·l'Arrêté·royal·du·09/01/2018·relatif·aux·biobanques.·Après·l'avoir·rempli·et·signé,·il·doit·être·envoyé·avec·les·annexes·par·courrier·recommandé·à·l'adresse·suivante·:¶

Agence·fédérale·des·médicaments·et·des·produits·de·santé·–·AFMPS¶
Eurostation·II¶
Matériel·corporel·humain¶
Place·Victor·Horta·40/40¶
1060·BRUXELLES¤

| 1°·Données·concernant·la· |
|---|





afmps
agence fédérale des médicaments et des produits de santé
Cellule Matériel Corporel Humain

Philippe De Buck
Tél. : +32 2 528 40 00
e-mail : biobanks@fagg-afmps.be

Agence fédérale des médicaments et des produits de santé
Avenue Galilée 5/3
1210 Bruxelles
www.afmps.be


FIOIG Biobanque
Avenue de Sumatra 6
1180 Uccle
Belgique

| Votre lettre du | Vos références | Nos références | Annexe(s) | Date |
|---|---|---|---|---|
| | | 0000 | 0 | |

**Objet:** Notification établissement biobanque

Madame, monsieur,

J'accuse bonne réception de votre notification concernant votre biobanque conformément à l'art. 3 de l'arrêté royal du 9 janvier 2018 relatif aux biobanques. Nous avons reçu la notification en date du **31-05-22** et nous vous confirmons que le dossier est complet et recevable.

En date du **09-06-2022** le numéro de notification **BB220008** est accordé à la biobanque sise à
FIOIG Biobanque
Avenue de Sumatra 6
1180 Belgique

L'exploitant de la biobanque est : **Fondation 101 Génomes**
le gestionnaire du matériel corporel humain au sein de la biobanque est : **Verboogen, Michel**

Ce numéro de notification vous est accordé sans préjudice de toutes consultations ou vérifications ultérieures relatives à la conformité aux dispositions de l'Arrêté Royal 9 janvier 2018 relatif aux biobanques.

Toute modification aux renseignements fournis la pour la présente notification ou toute cessation temporaire ou définitive envisagée des activités de la biobanque doit, conformément l'art. 4 l'arrêté Royal du 9 janvier 2018, immédiatement être signalée à l'Agence Fédérale des Médicaments et des Produits de Santé. Ces informations peuvent être communiquées soit par lettre soit par courriel adressée à l'adresse biobanks@fagg-afmps.be, toujours en mentionnant le numéro de notification.

Veuillez agréer, Madame, Monsieur, l'expression de nos salutations distinguées,

afmps fagg
Digitally signed by
Philippe De Buck
(Signature)
Date: 2022.06.10
17:41:24 +02'00'

Philippe De Buck,
Chef de division autorisation.


# Bioinformatic storage

# Microsoft Azure & Data Twin

## Cloud Storage


After legal examination and regular contact at Microsoft (both at European and Belgian level), **Microsoft Azure** was chosen as the partner to host the data. Mainly because Microsoft offers the **safest and most regulatory compliant current Cloud option** for genomic storage on the market as of today.

T**he F101G opened its Cloud (Data Lake)** and since **October 2020** we have been working on the development of this facility with different consultants.

The F101G Data Lake now already allows to host and store genomic data securely in the cloud.

This solution will facilitate at a later stage access for as many researchers as possible.

# Genomics in the Cloud

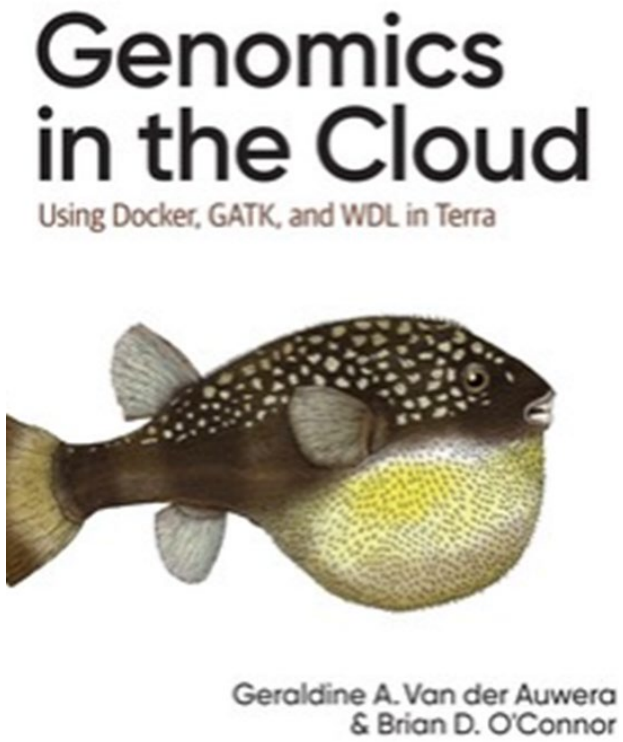
**Géraldine Van Der Auwera (Broad Institute MIT/Harvard)**

**Géraldine Van der Auwera** (Broad Institute MIT/Harvard - Author of *Genomics in the Clouds*) has accepted to be involved in the set-up of our **Genomic Cloud and its optimization**, keeping in mind the numerous interactions required for fair genomics activities.

Until now, Géraldine has mainly developed her expertise in the Google environment. She was looking for a genomic project to replicate what she did on Google Cloud Platform in the Microsoft Azure world. Our project is a perfect fit for her and she will work with us to implement our genome storage solution on Azure.

We have bi-monthly meetings with Géraldine to advance our development.

We are considering structuring our data by aligning them with ***Terra* data model**, a cloud-native platform for biomedical researchers to access data, run analysis tools, and collaborate.



# Emma Verkinderen

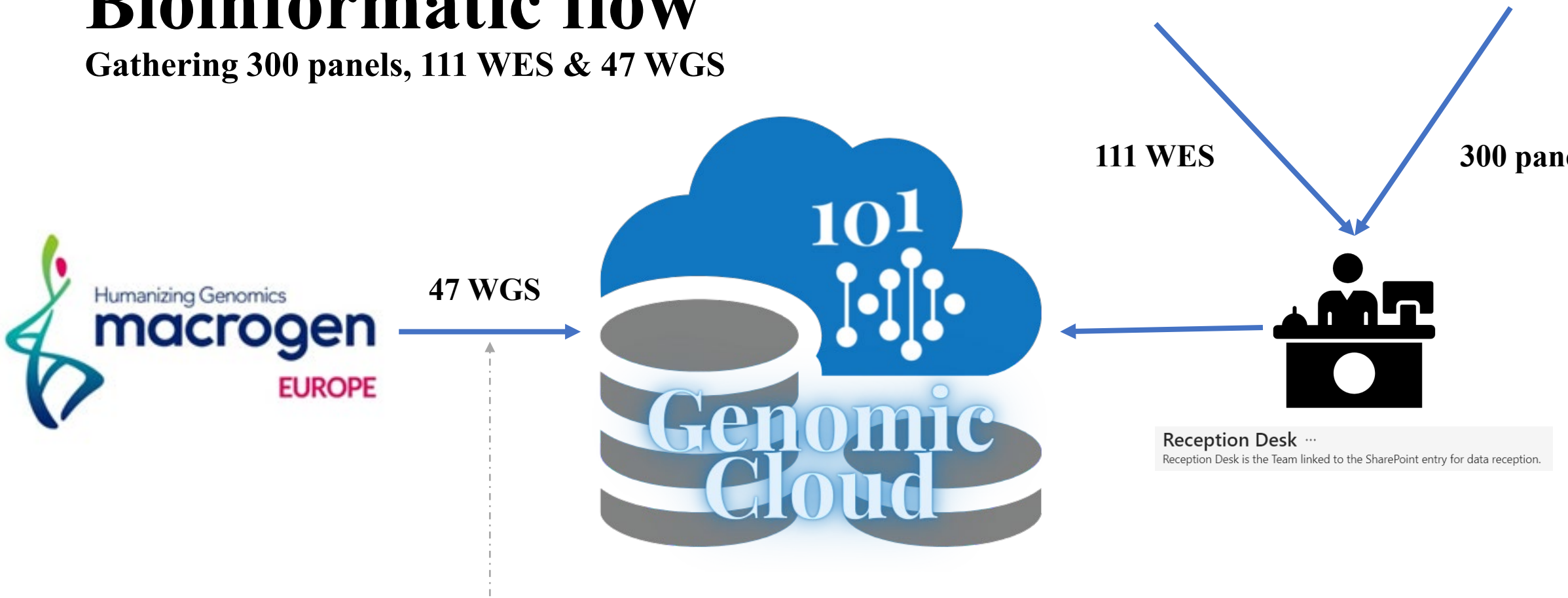
**G4BXL**


Bioinformatician **Emma Verkinderen**, who is engaged by Prof. Tom Lenaerts in the context of **Genome4Brussels**, has become involved with this component of the project, notably by helping to define the requirements for the hosting solution in order to ensure that the Cloud solution will allow to integrate and use AI tools developed in the Marfan context.

https://www.f101g.org/en/genome4brussels-par-emma-verkinderen/

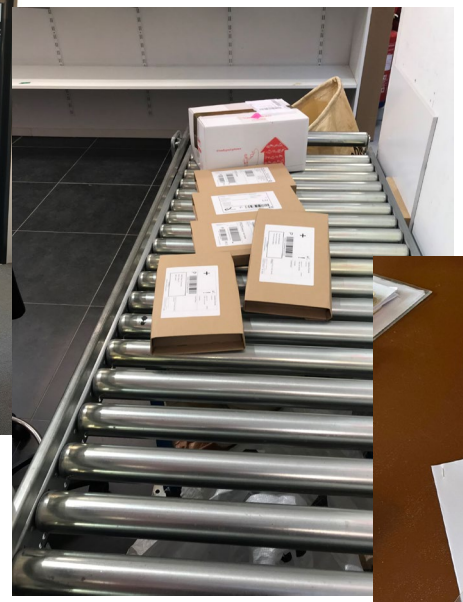
# Bioinformatic flow

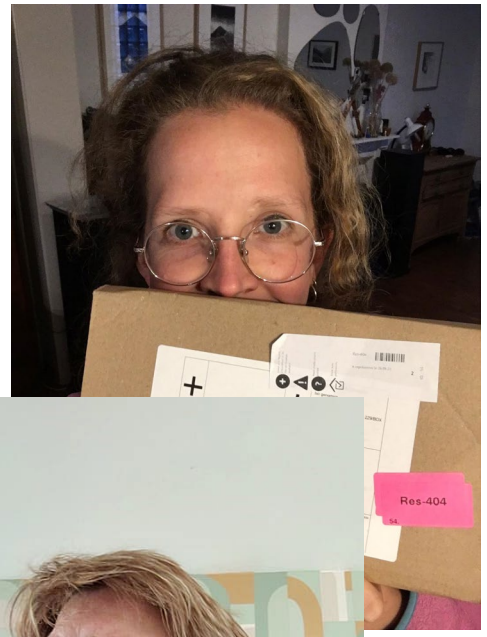
**Gathering 300 panels, 111 WES & 47 WGS**




*First ever interconnection between macrogen and azure*

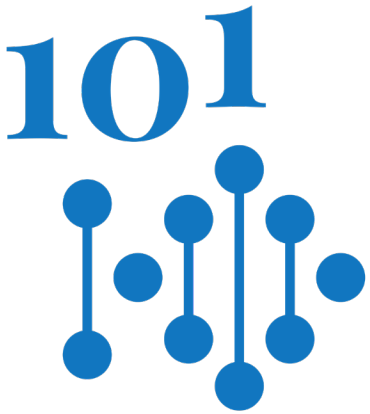
| ID |
| --- |
| participant_70 |
| participant_78 |
| participant_81 |
| participant_82 |
| participant_83 |
| participant_86 |
| participant_88 |
| participant_89 |
| participant_90 |
| participant_91 |
| participant_92 |
| participant_93 |
| participant_94 |
| participant_102 |
| participant_106 |




+ **15 testers** who tested the kits in Belgium, France, Luxembourg, the Netherlands, Slovakia, Sweden, Austria and Denmark (= 62).

Will there also be Spanish and German testers after this seminar?




# Deployment of the F101G Genomic Cloud

# Deployment of the F101G Genomic Cloud


Emma Verkinderen

Interuniversity Institute of Bioinformatics Brussels

VASCERN GEMS seminar 20/01/2023

# Outline of this presentation

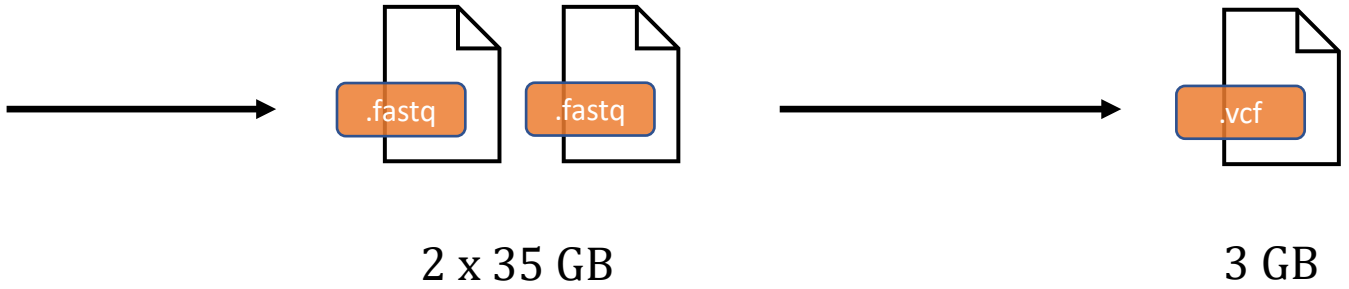
1. Introduction
   - Genomic data
   - Cloud
   - Data lake

2. Our road to a Genomic Cloud in Microsoft Azure
   - Mapping the requirements
   - Set-up process with Cloud architect Colby Ford

3. Next steps

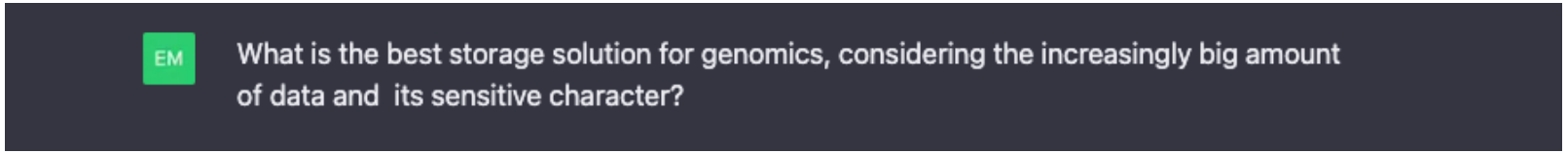
# 1. Introduction

# Sequencing DNA samples generates huge amounts of **genomic data**




⇨ 135 GB of **sensitive, personal** data for each participant

# Let’s ask our new friend ChatGPT



# “The Cloud” ?

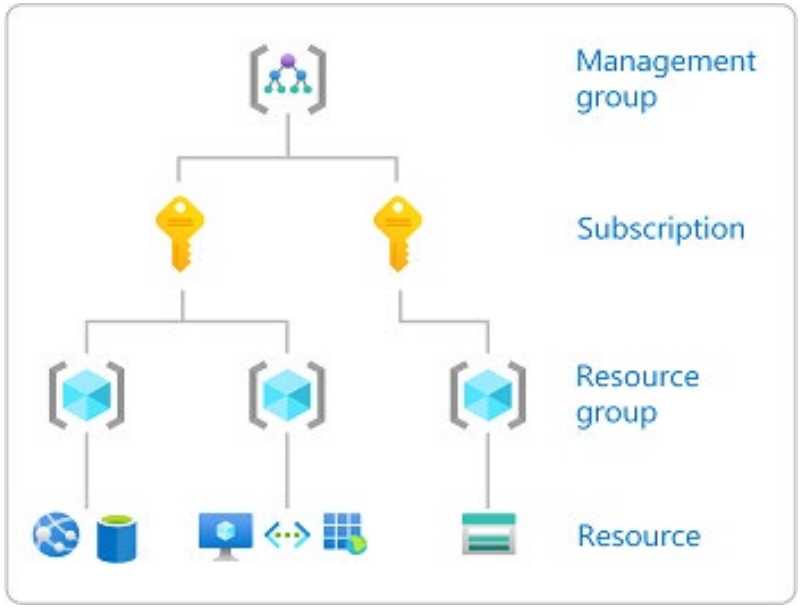
On-premises hosting

https://www.storagereview.com/news/home-lab-deep-dive-an-educators-perspective

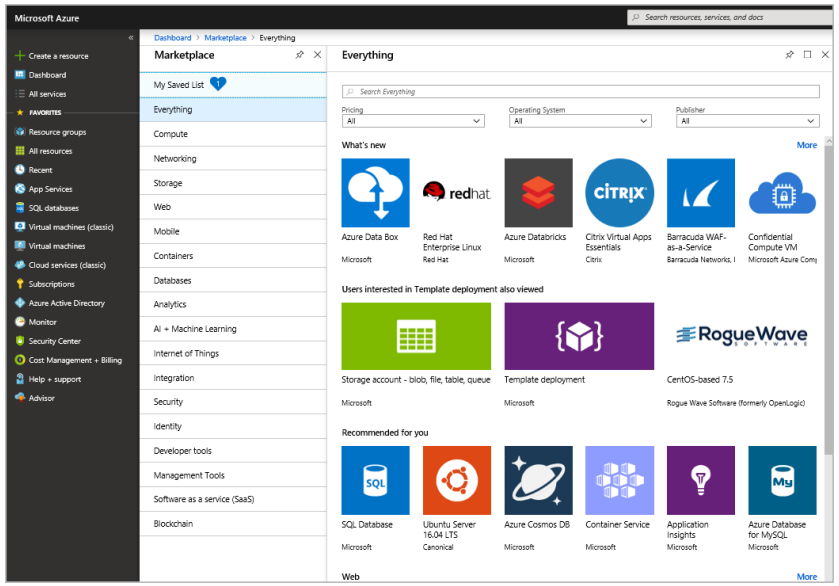
Public Cloud (IaaS: Infrastructure as a Service)

https://www.microsoft.com/nl-be/microsoft-365/blog/2019/07/25/microsoft-office-365-now-available-from-new-south-africa-cloud-datacenters/attachment/2283/

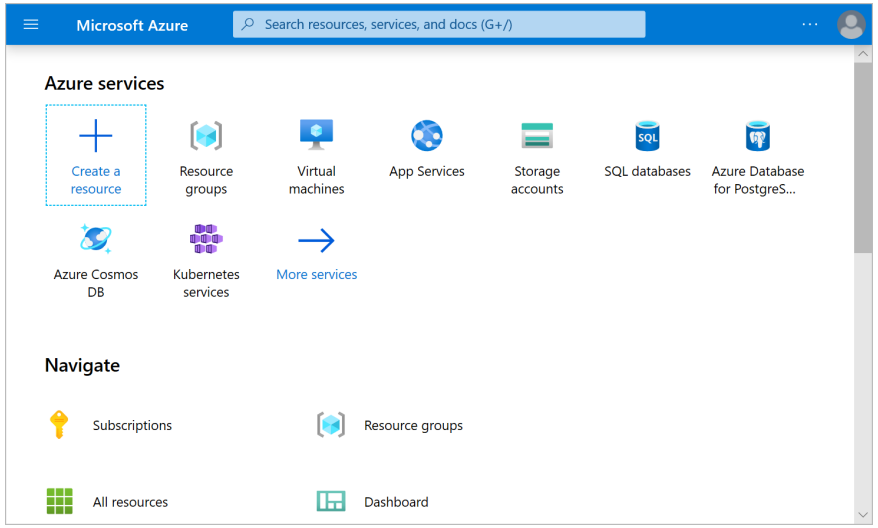
# Microsoft Azure 101




https://learn.microsoft.com/nl-nl/azure/role-based-access-control/scope-overview



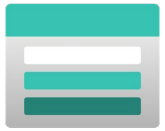

Marketplace for Azure Services



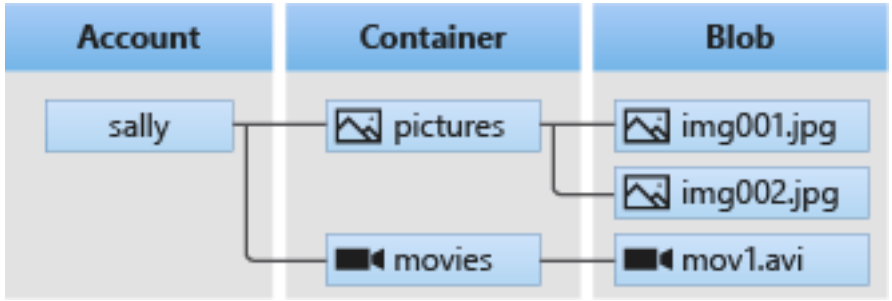

Azure Portal

# A “data lake” to host our genomic data in the cloud

- = repository for storing large amounts of heterogenous data



- In Azure: Storage Account
  - Blob storage service




https://learn.microsoft.com/en-gb/azure/storage/blobs/storage-blobs-introduction

# 2. Roadmap to a Genomic Cloud in Azure

# 2.1 Mapping the requirements

- Swim-lane diagrams
  - Actors & actions

- Paths of **Data collection**
  - Sources?
  - Data types?

  - Modules:
    - Personal information & consent management
    - Phenotypic data
    - Genomic data incl. variant calling pipeline
    - (Externally provided data)

# Personal information and consent data

# Phenotypic & genomic data

# Cohorts from external research groups

2 cohorts received

- 111 exomes from prof. Catherine Boileau (Paris)
- 300 gene panels from prof. Bart Loeys (UA)

# 2.1 Mapping the requirements

- Swim-lane diagrams
  - Actors & actions

- **Data collection**

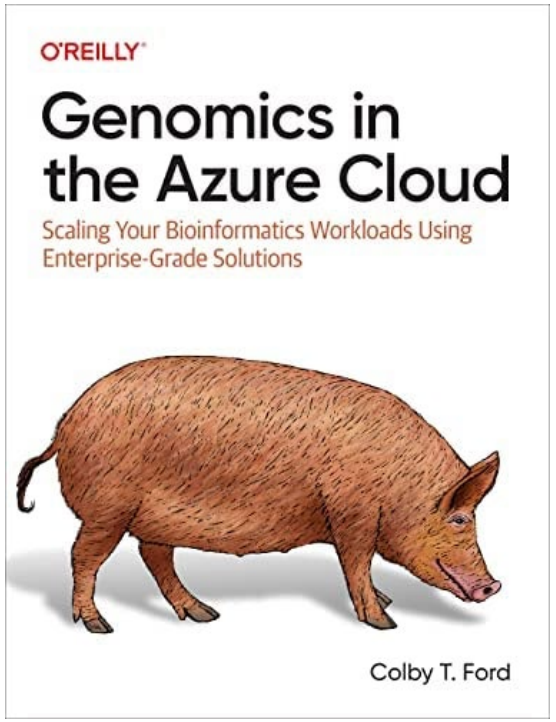
- Procedures for **data access**
  - Participants
  - Healthcare providers
  - Researchers: single participant or cohort

# 2.1 Mapping the requirements

Data access dashboard

# 2.2 Set-up process guided by Colby Ford

1. Data lake deployment
   - Lifecycle management -> storage tiers
   - Organization & naming conventions

# Defining the data lake organization & naming conventions

Storage account (with hierarchical namespace enabled): **stocoredatalake001prd**

↳ Container: **datalake**

↳ Top directory: **bioinformatics_data**

- Self-explanatory
- Robust
- Adapted to possible future analyses

# 2.2 Set-up process guided by Colby Ford

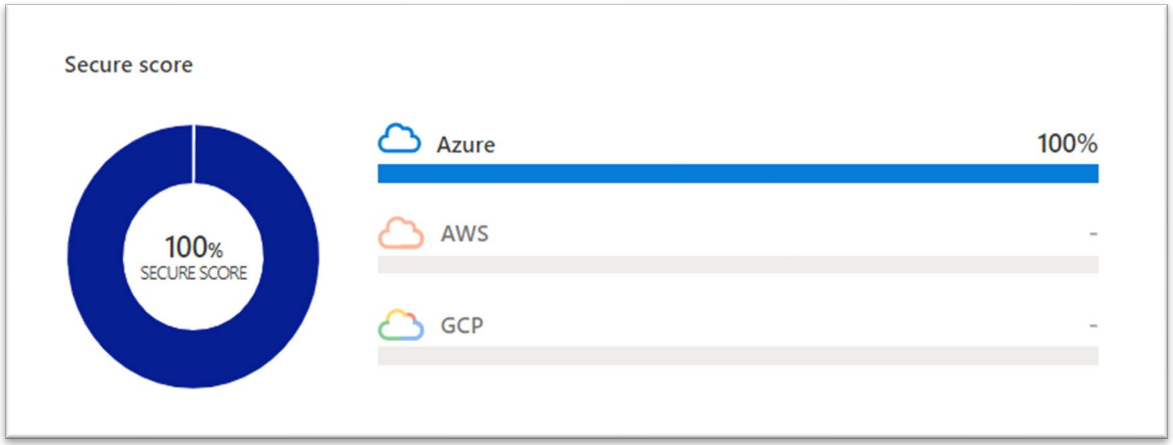
1. Data lake deployment
2. Data lake integration pipelines
   - Phenotype data from GEMS app
   - Genomic data from Macrogen
   - External cohorts

# 2.2 Set-up process guided by Colby Ford

1. Data lake deployment

2. Data lake integration pipelines

3. Security & compliance
   - Security consultant Eric Raepers
     - Azure Active Directory recommendations
     - Deployment recommendations (networking)
     - Logging, analytics & alerting
   - Microsoft Defender for Cloud
     - Secure score of 94-100%
     - Regulatory compliance policies



# 3. Next steps: using the data!

# Set-up process guided by Colby Ford

1. Data lake deployment
2. Data lake integration pipelines
3. Security & compliance
4. Visualization module
   - Viewer for DICOM images (CT/MRI scan)

# Set-up process guided by Colby Ford

1. Data lake deployment
2. Data lake integration pipelines
3. Security & compliance
4. Visualization module
5. Integration of tools for bioinformatic analyses

Nassim Versbraegen

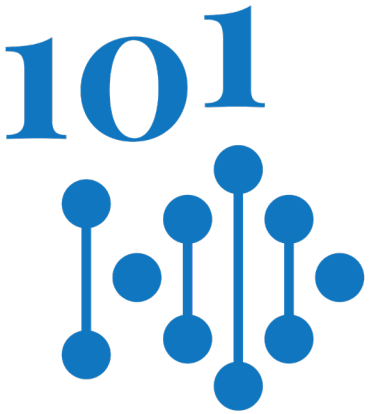
# Thank you! Questions?

ULB UNIVERSITÉ LIBRE DE BRUXELLES

101 Genomes Foundation Genomics for Rare Diseases

VUB VRIJE UNIVERSITEIT BRUSSEL

funded by innoviris .brussels



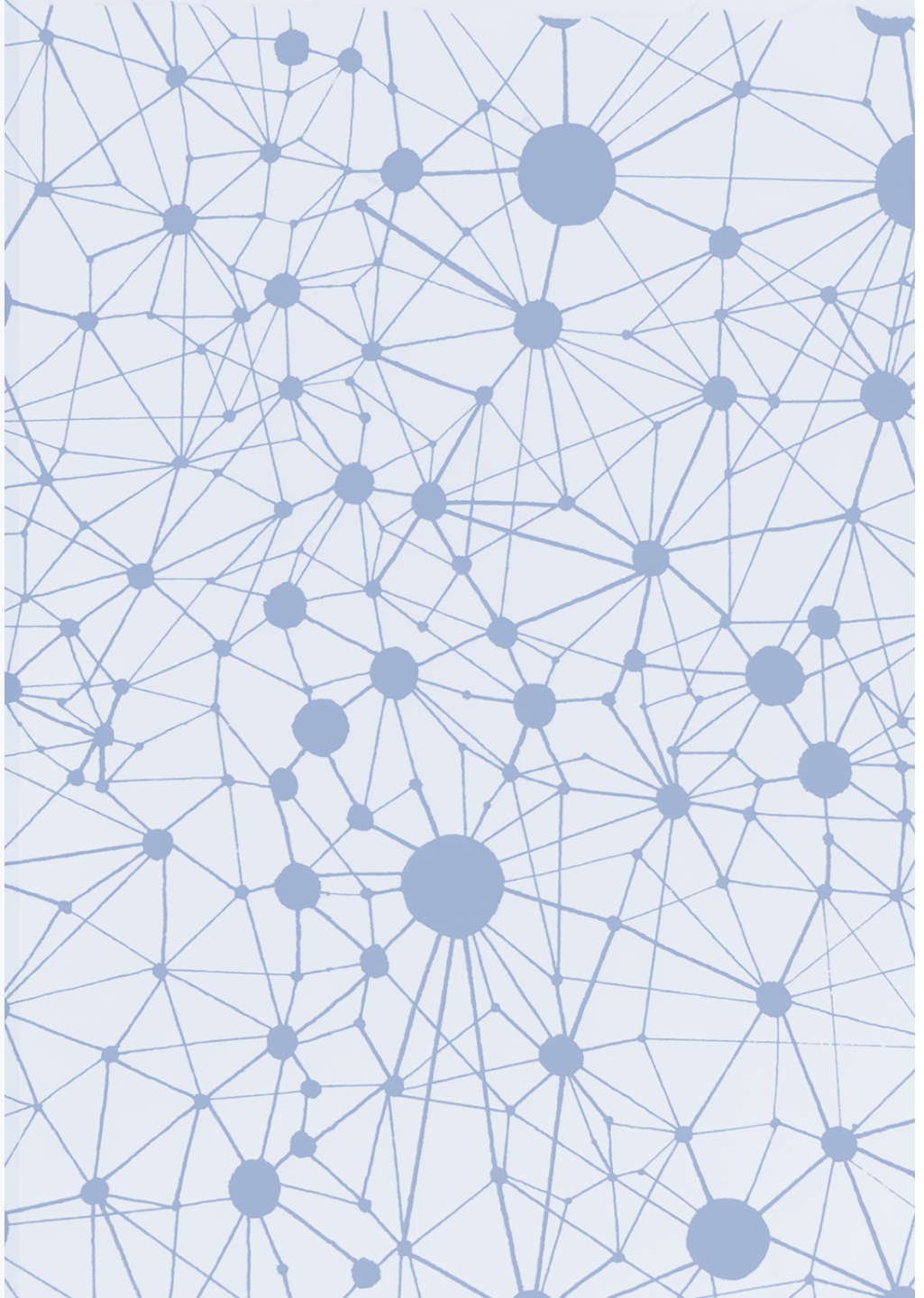

# Overview of the oligogenic machine learning research at (ib)²

# OVERVIEW OF THE OLIGOGENIC MACHINE LEARNING RESEARCH AT THE INTERUNIVERSITY INSTITUTE OF BIOINFORMATICS IN BRUSSELS

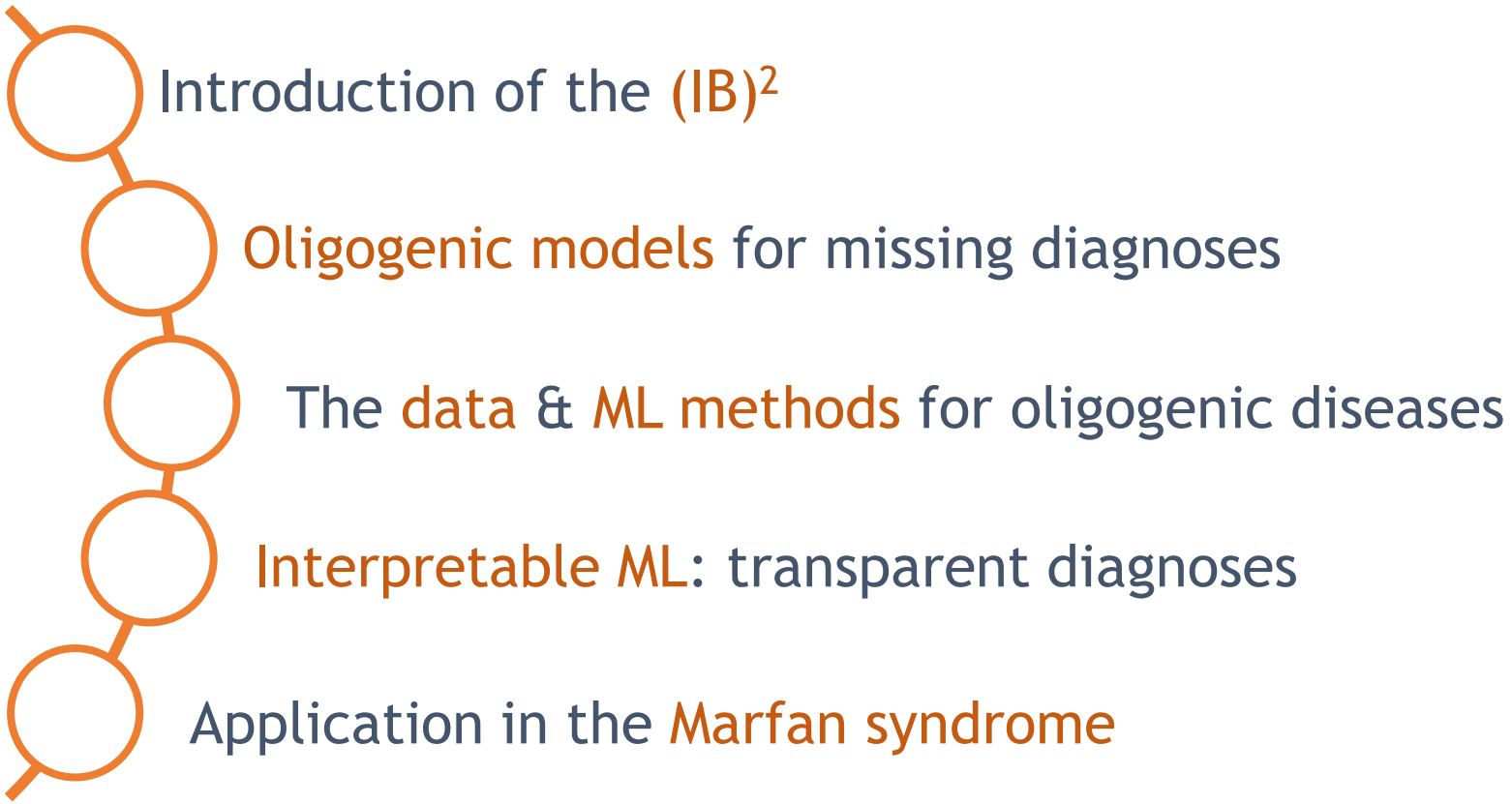
**Sofia Papadimitriou**
*F.R.S-FNRS Postdoctoral Researcher*

Université Libre de Bruxelles &
Ghent University

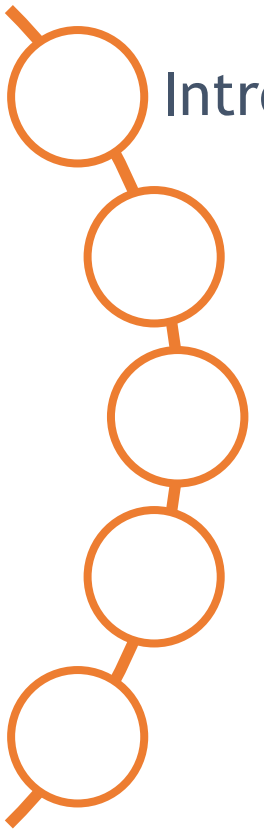
VASCERN Exchange Visit, 20/01/2023



# Overview


Introduction of the (IB)²
Oligogenic models for missing diagnoses
The data & ML methods for oligogenic diseases
Interpretable ML: transparent diagnoses
Application in the Marfan syndrome

# Overview



Introduction of the $(IB)^2$

# The team of $(IB)^2$


## Directors

Matthieu Defrance
*Professor, ULB*

Sophie de Buyl
*Professor, VUB*

44 Principal investigators
7 Senior researchers
17 PhD students
2 Staff members

>200 Publications
15 Ongoing projects

# Overview of the oligogenic team

Tom Lenaerts
*Professor, ULB*

Ann Nowé
*Professor, VUB*

Sofia Papadimitriou
*Postdoctoral researcher*

## Mission

apply novel computational methods to decipher the genetic architecture of oligogenic diseases

Charlotte Nachtegael
*PhD student*

Simon Boutry
*PhD student*

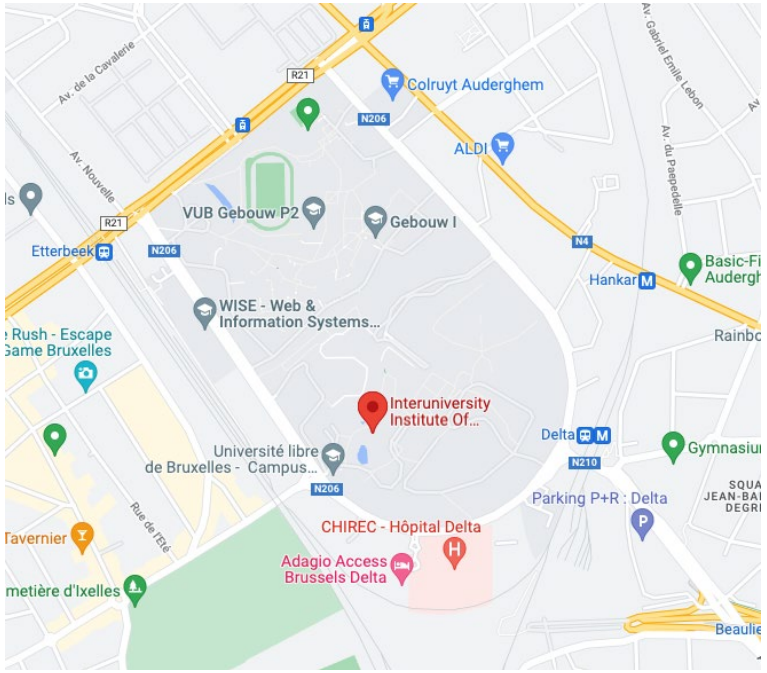
Nassim Versbraegen
*PhD student*

Alexandre Renaux
*PhD student*

Barbara Gravel
*PhD student*

Emma Verkinderen
*Technician*

# Contact details




Interuniversity Institute of Bioinformatics in Brussels (IB)2,
ULB, La Plaine Campus,
Triomflaan, BC Building, 6th floor, CP 263
1050 Ixelles, Belgium

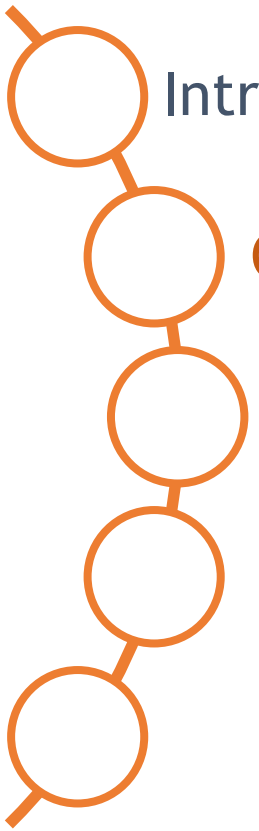
https://ibsquare.be/

@BrusselsBioInfo

firstname.lastname@ulb.be

directors:
Matthieu.Defrance@ulb.be
Sophie.de.Buyl@vub.be

# Overview

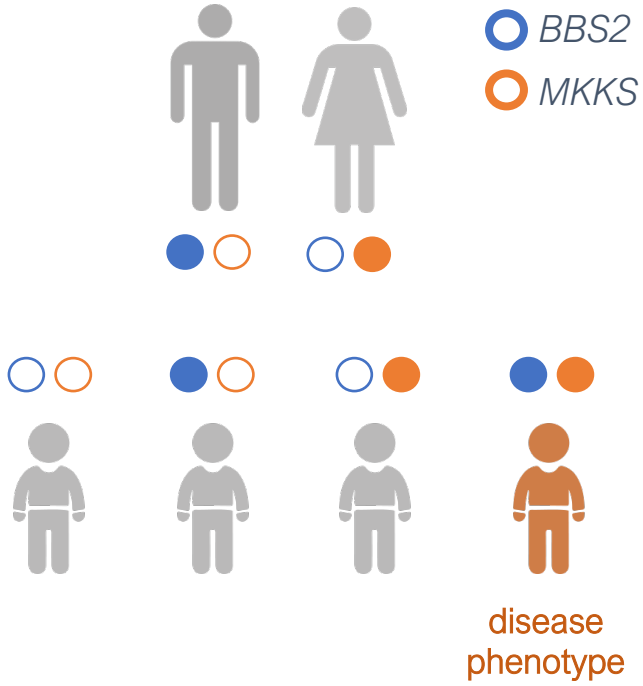


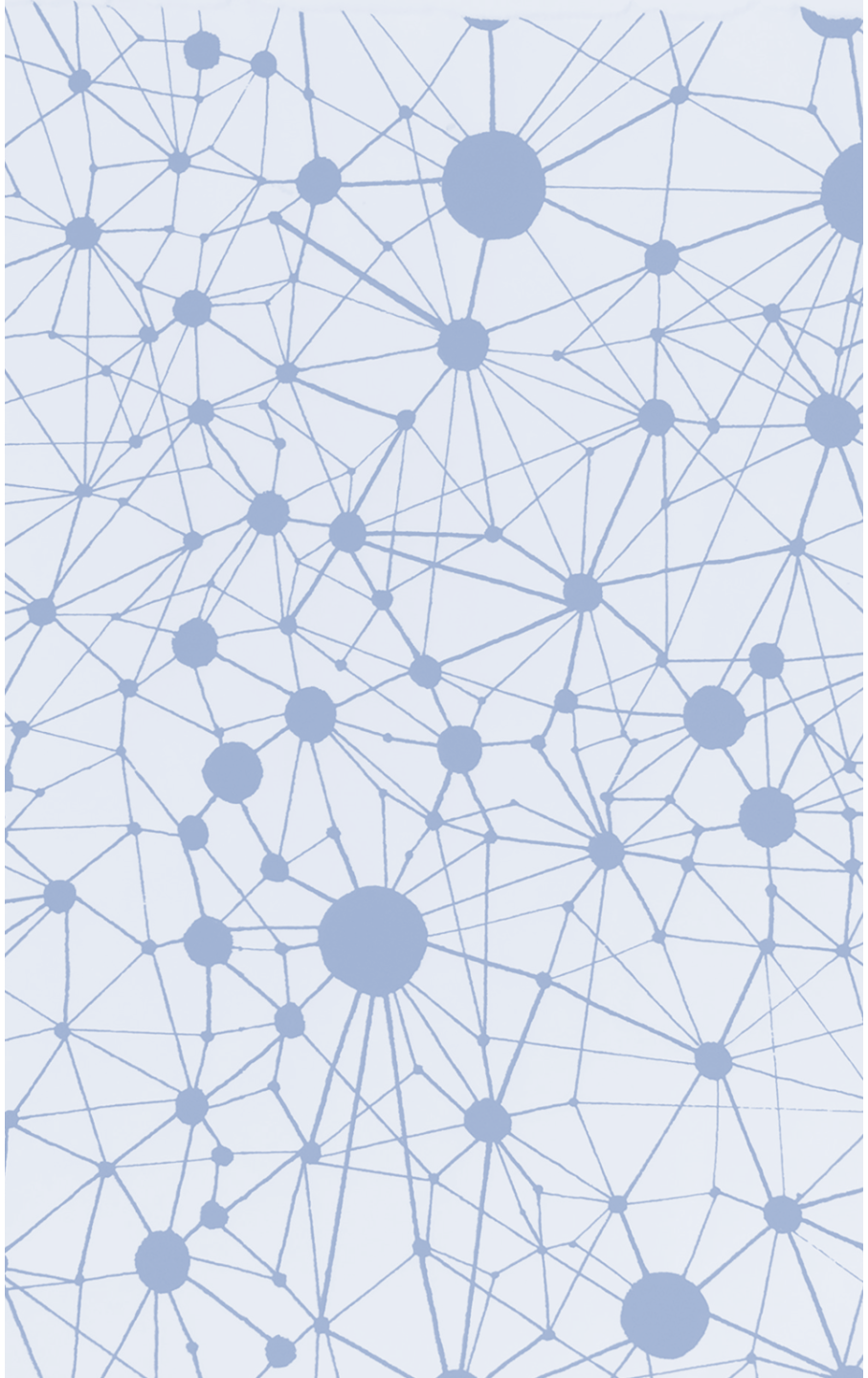
Introduction of the $(IB)^2$

Oligogenic models for missing diagnoses

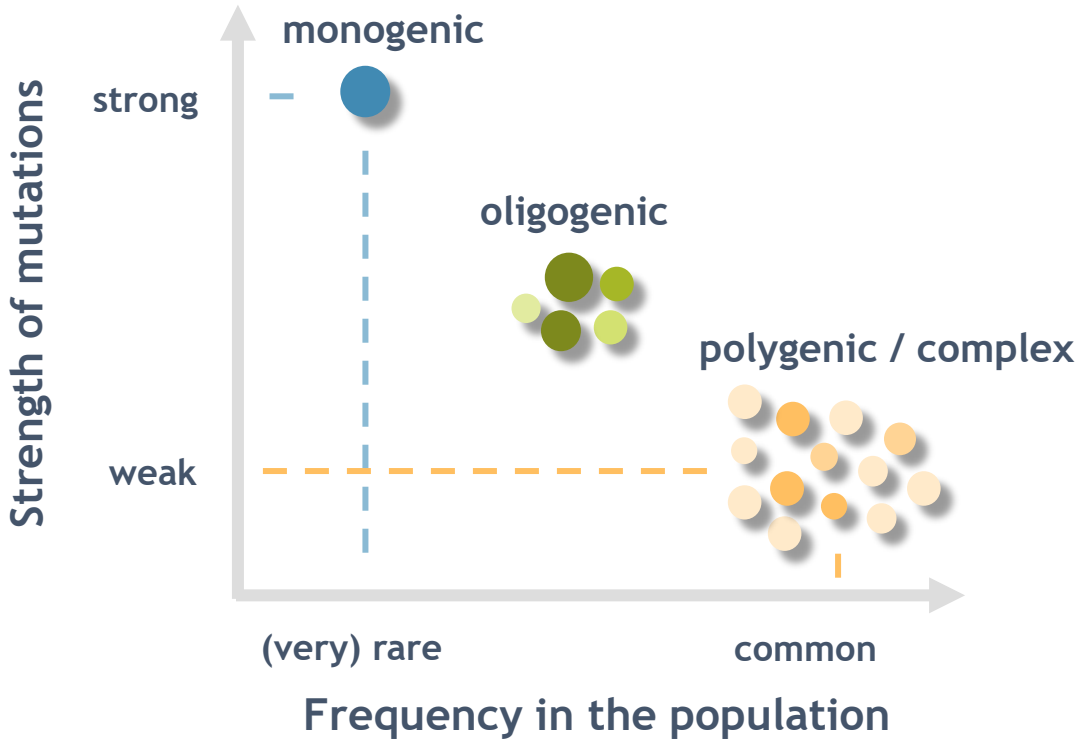
# Oligogenic diseases

Mutations in several genes can better explain the phenotype of a patient, compared to one gene alone.



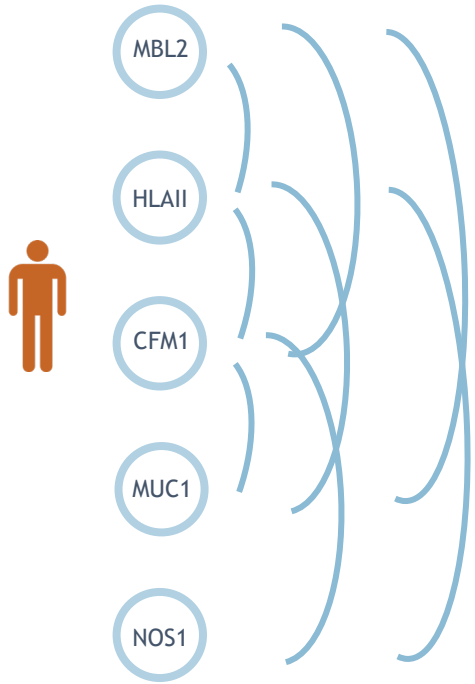
# Oligogenic diseases in the middle of a continuum




McCarthy, *et al.* (2008). *Nature reviews genetics*. 9(5), 356.

# Several challenges exist

high
dimensionality




1,000,000
single genetic
variations

$5 \times 10^{11}$
2-way
combinations

# Several challenges exist

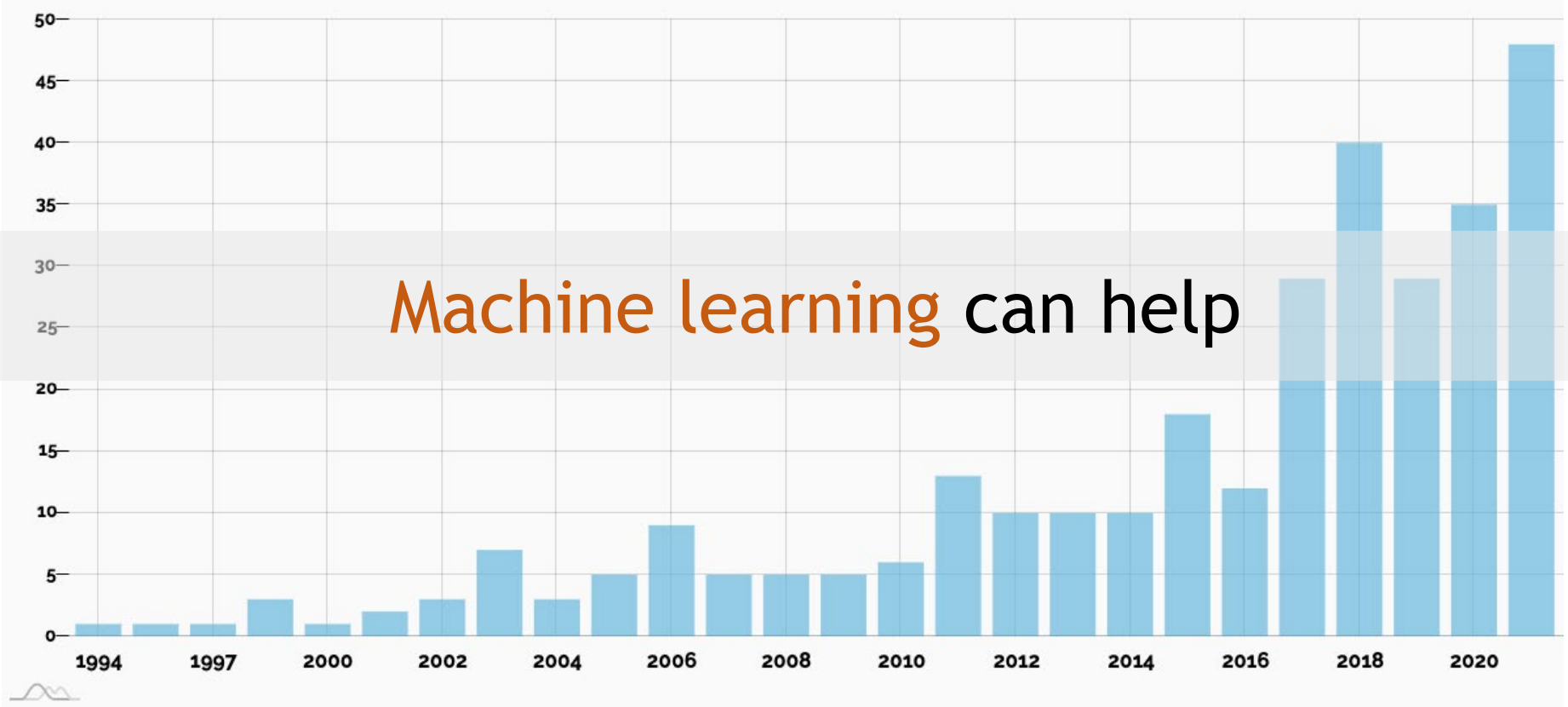
high dimensionality

need large cohorts

rare cases: not enough positive data

where do we look at in the genome?

# The data increases

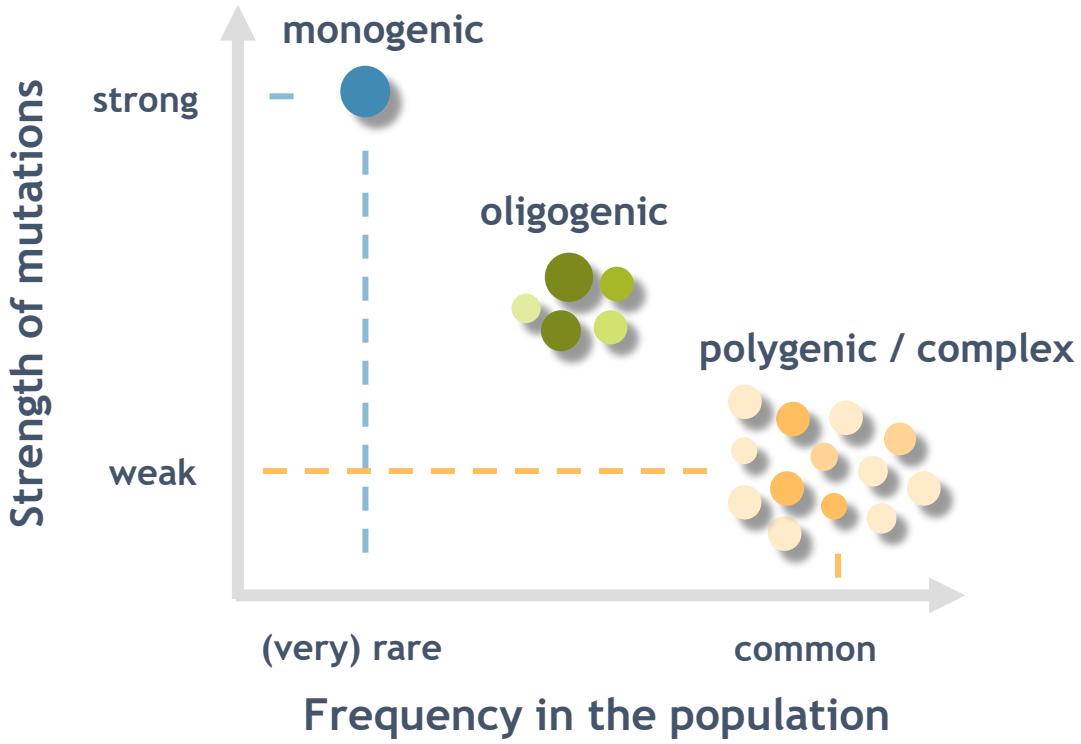



Machine learning can help

Number of publications reporting oligogenic cases

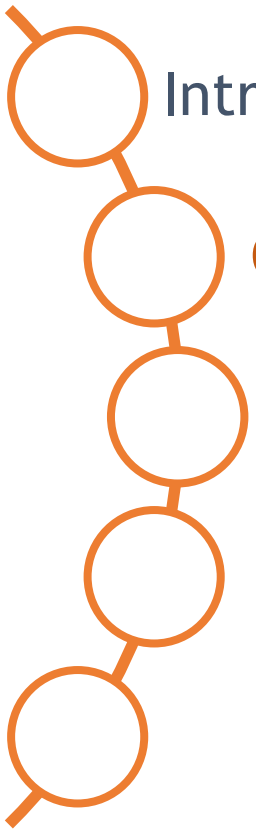
https://olida.ibsquare.be/

# Oligogenic diseases in the middle of a continuum




McCarthy, *et al.* (2008). *Nature reviews genetics*. 9(5), 356.

# Overview

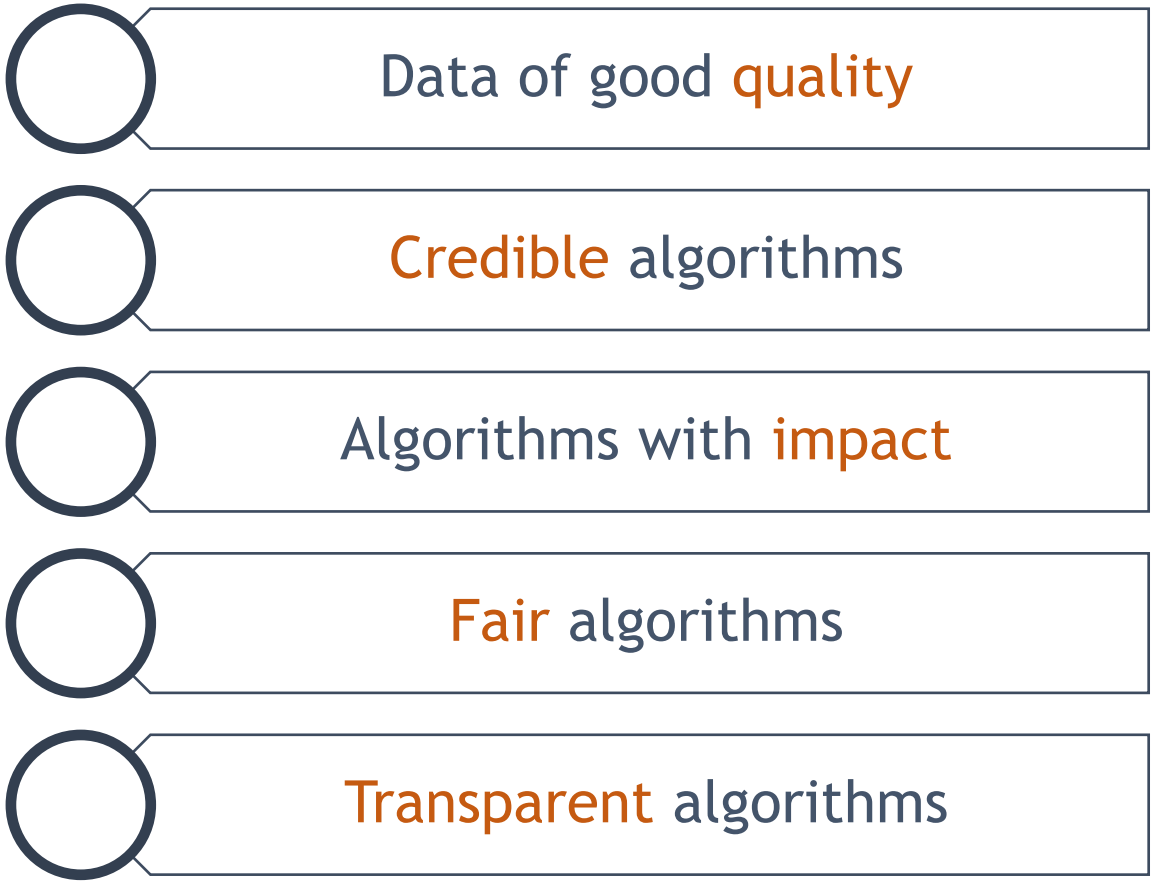


Introduction of the $(IB)^2$

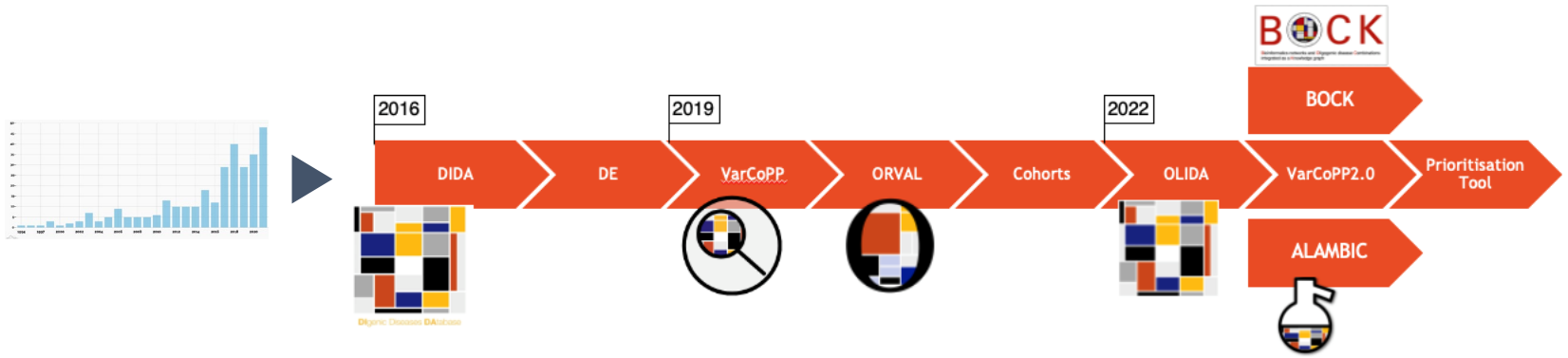
Oligogenic models for missing diagnoses

The data & ML methods for oligogenic diseases

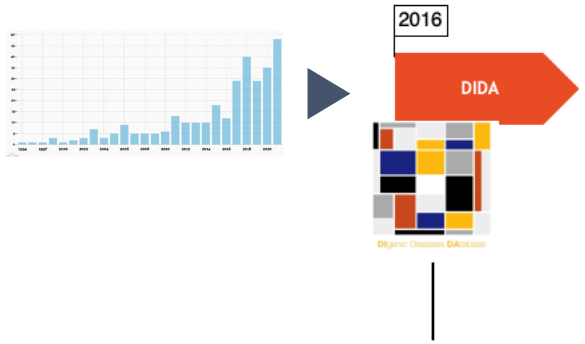
# Premises for the use of ML



# Developing ML methods for oligogenic diseases



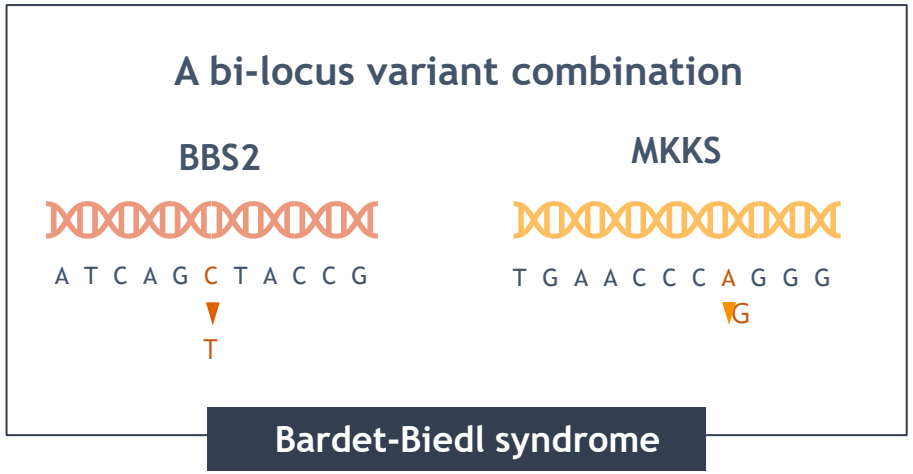
# Developing ML methods for oligogenic diseases

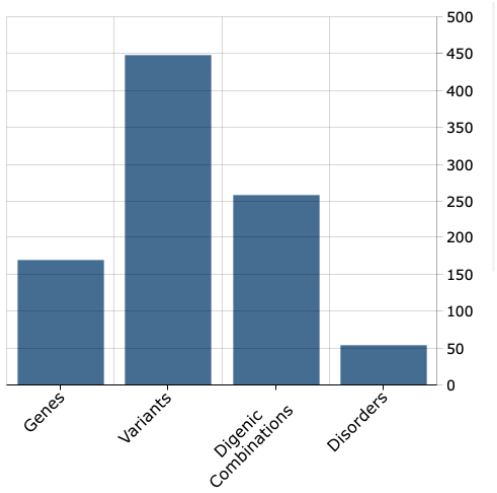



digenic
database

# DIDA: The Digenic Diseases Database

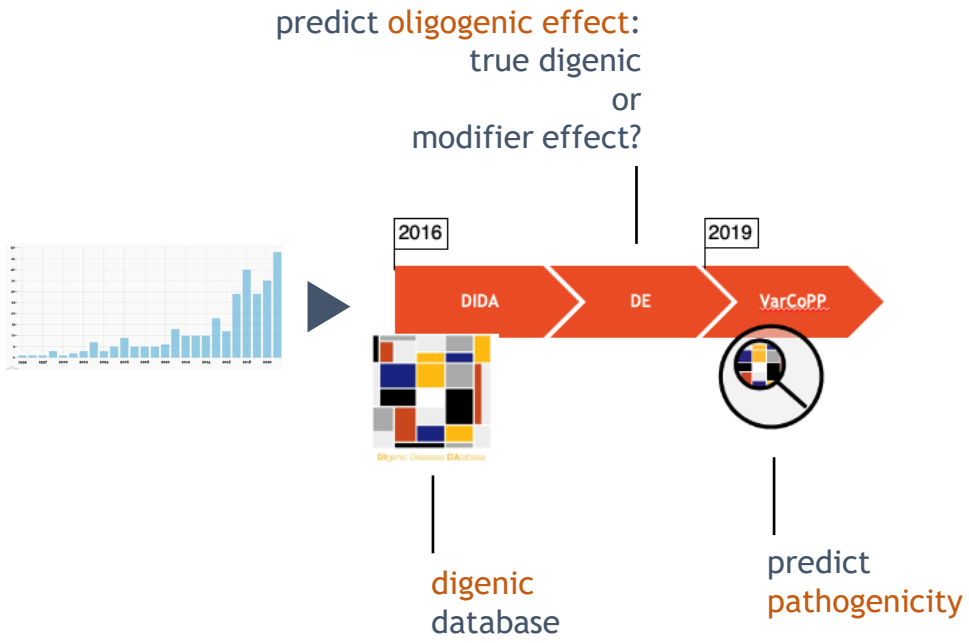
dida.ibsquare.be



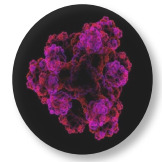




**258 bi-locus combinations**
causative for **54 diseases**

# Developing ML methods for oligogenic diseases



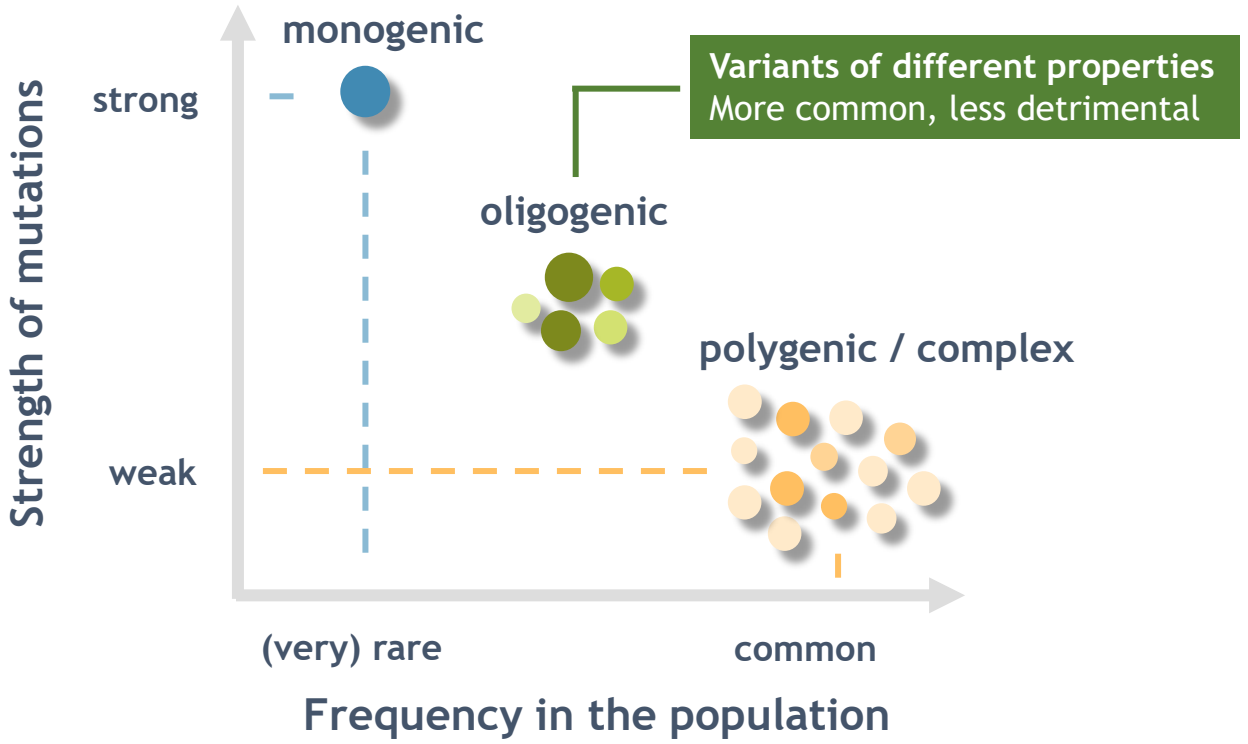
# Pathogenicity predictors need to move forward



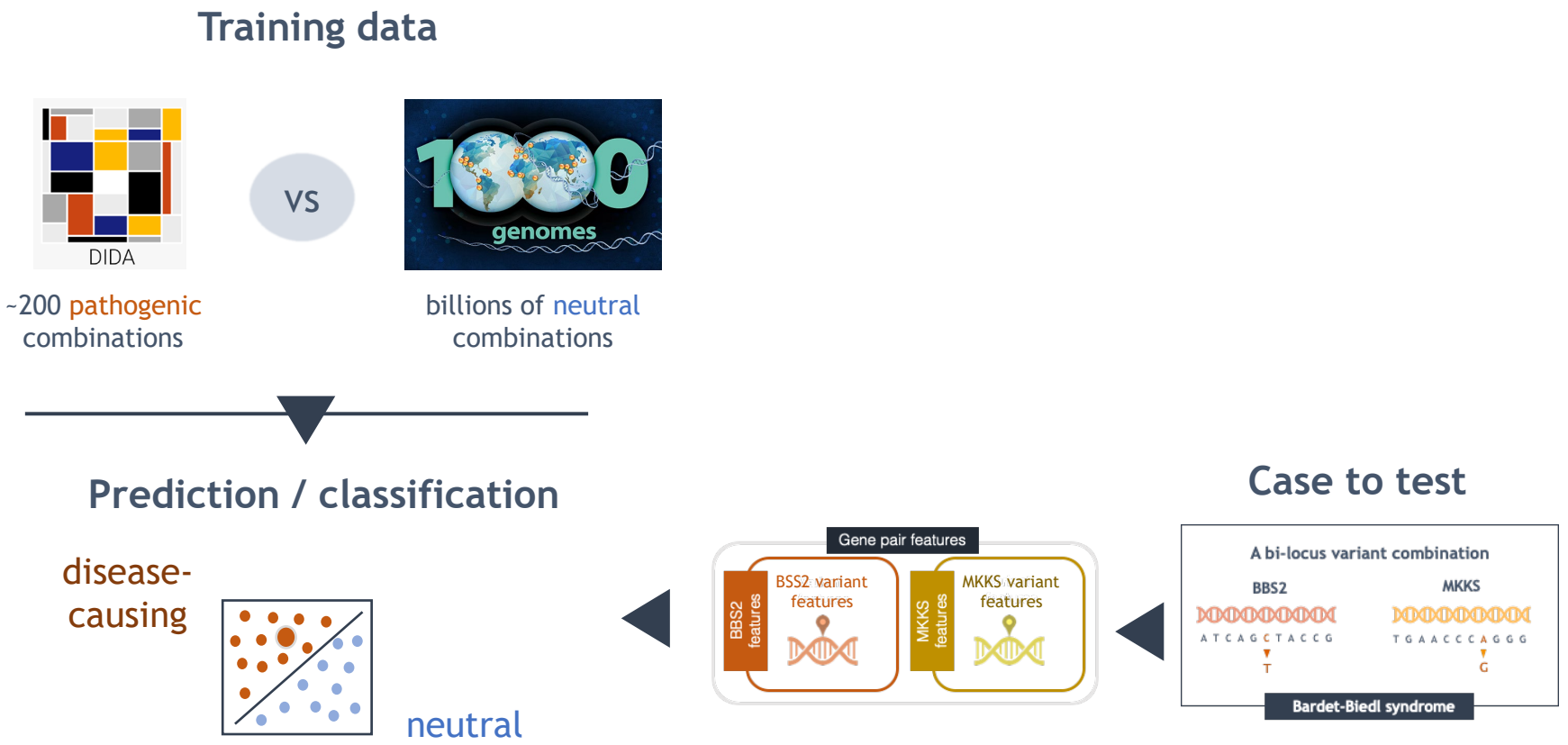
“Normal” …AGTG**C**GGTG… …S**A**V…

“Disease” …AGTG**A**GGTG… …S**E**V…

# Pathogenicity predictors need to move forward



# VarCoPP: predicting bilocus pathogenicity




Papadimitriou S., *et al.* (2019). *PNAS*. 116(24), 11878-11887.

# Performance depends on the disease

7% False Positives in random control combinations but …

**Bardet-Biedl syndrome**
a known digenic disease

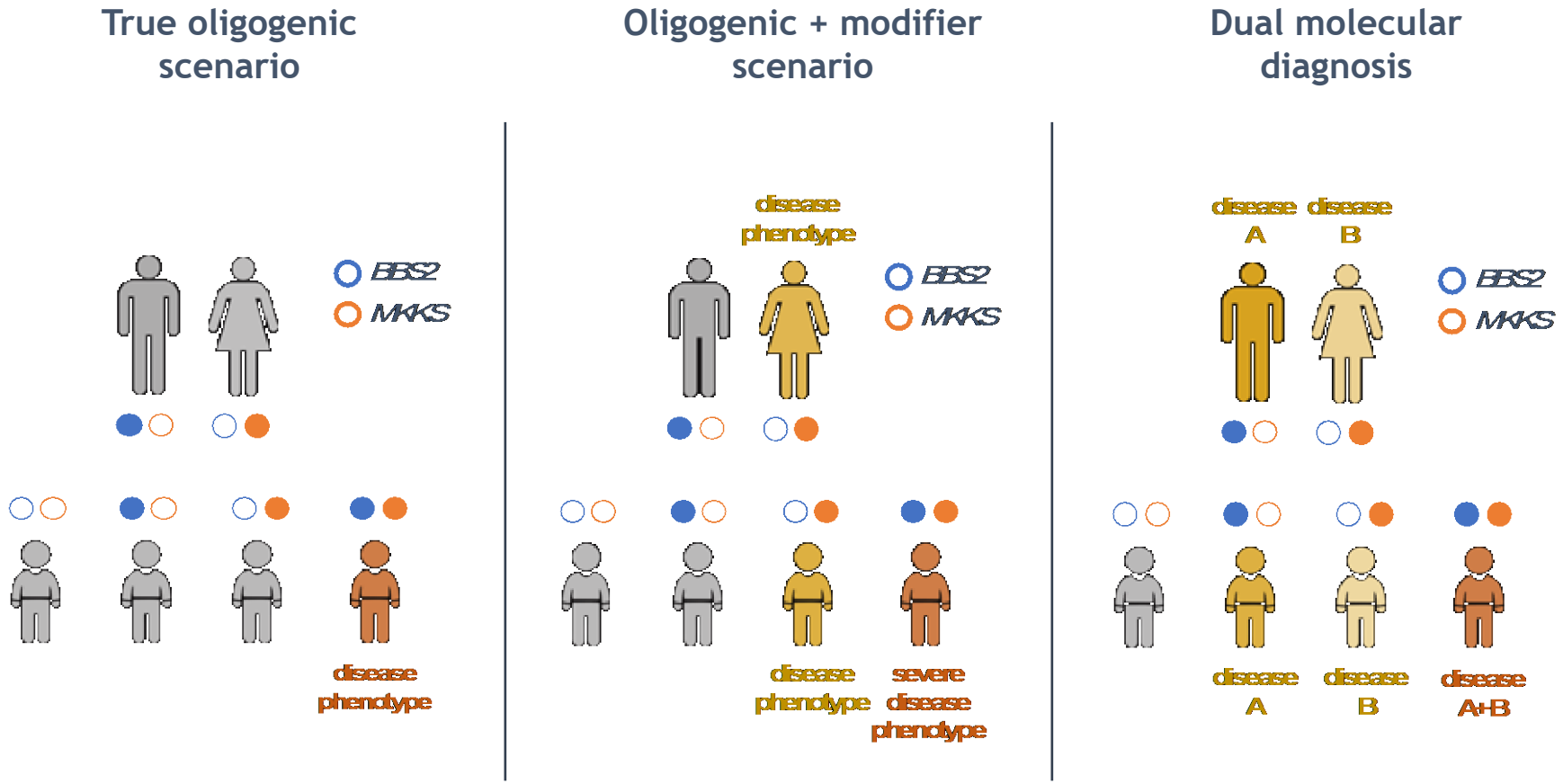
**13% False Positives**

**Autism**
spectrum of monogenic, oligogenic and polygenic causes

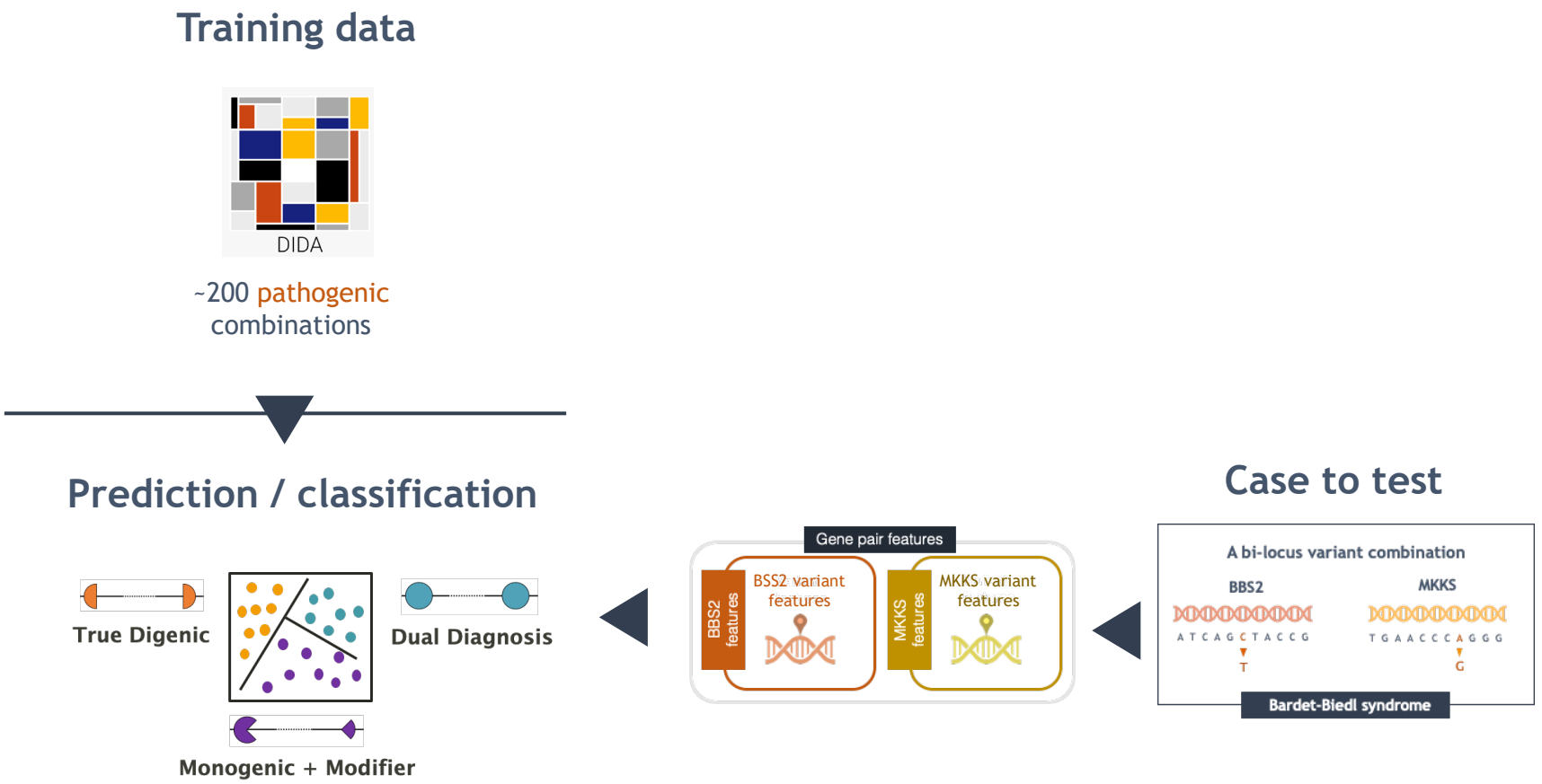
**2% False Positives**

Papadimitriou S., *et al.* (2019). *PNAS.* 116(24), 11878-11887.

# The Digenic Effect (DE) predictor

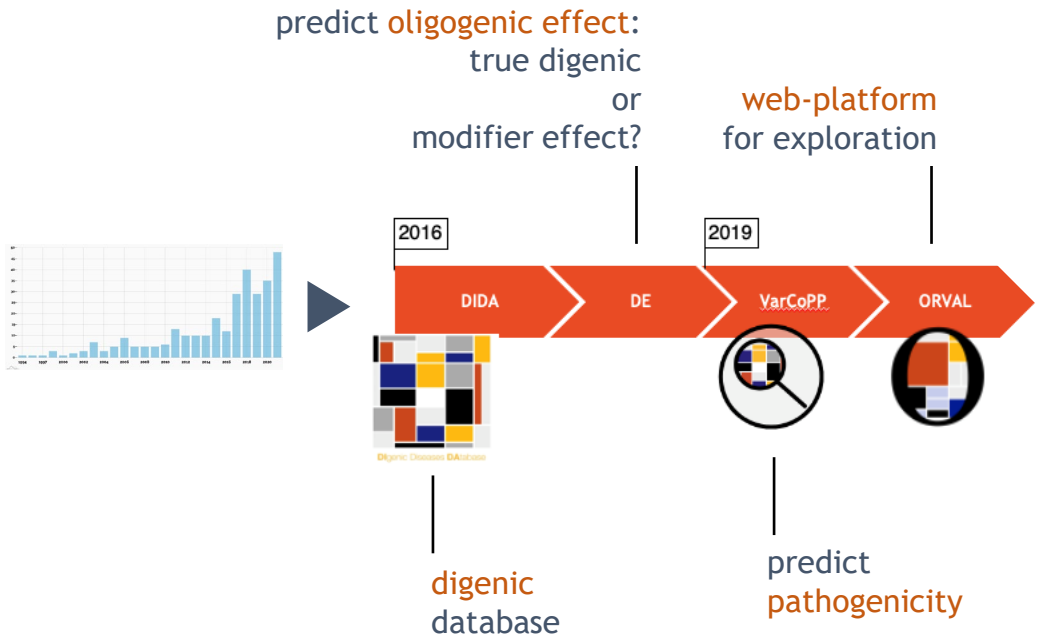


# The Digenic Effect (DE) predictor



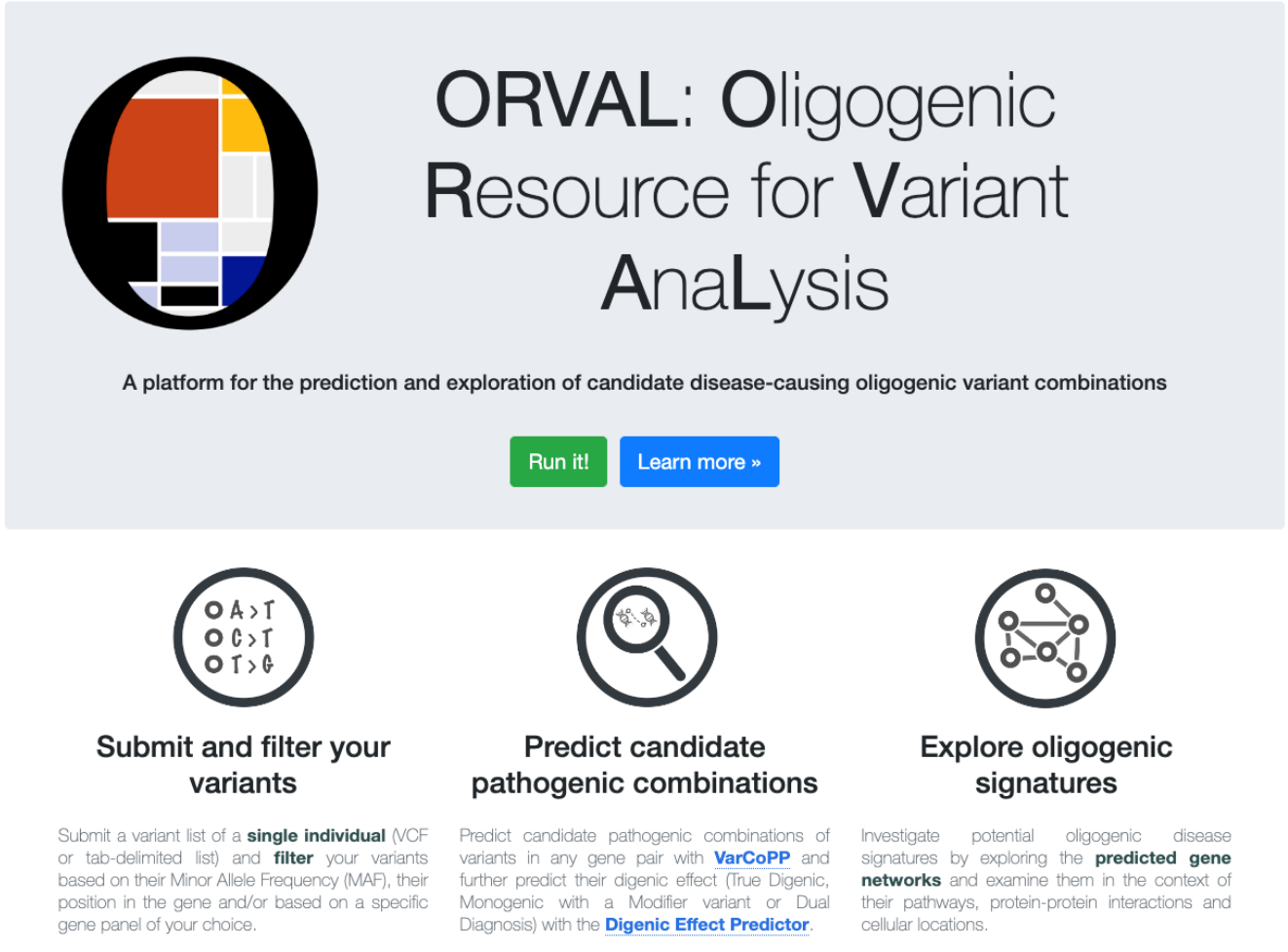

Versbraegen N. *et al* (2019) *Artificial Intelligence in Medicine*. 99:101690

# Developing ML methods for oligogenic diseases



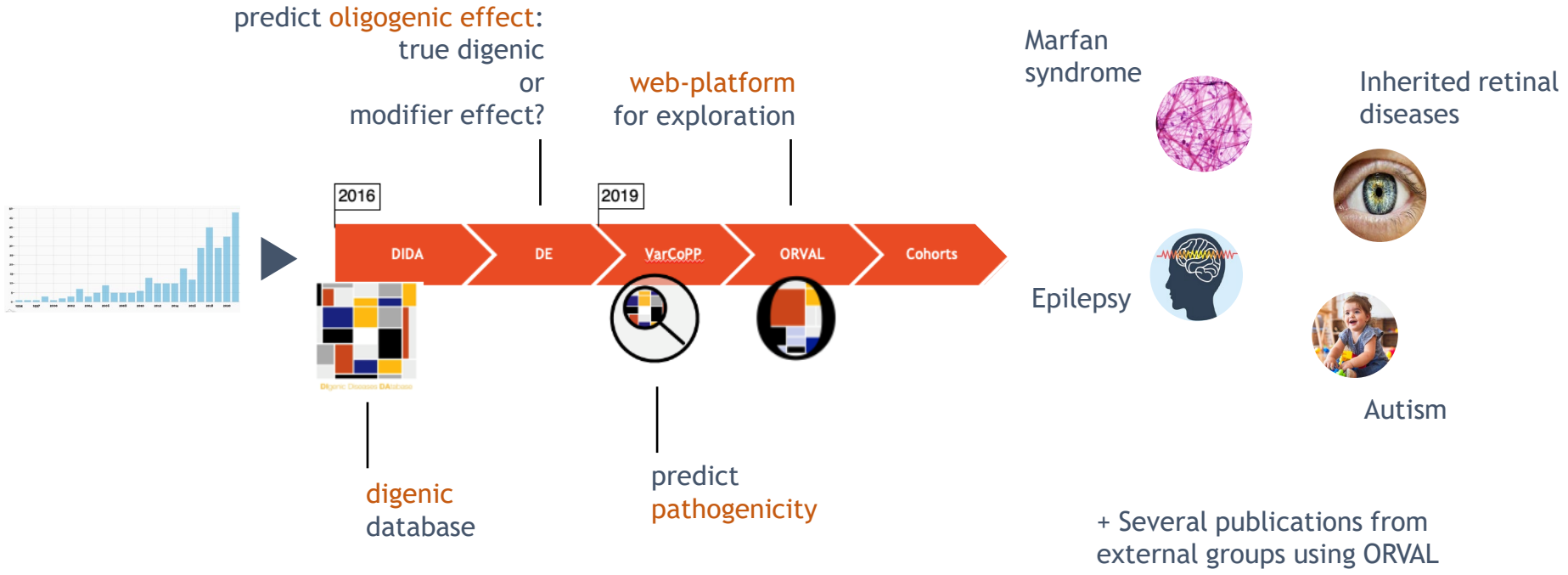
# ORVAL: a web-platform for oligogenic exploration

https://orval.ibsquare.be

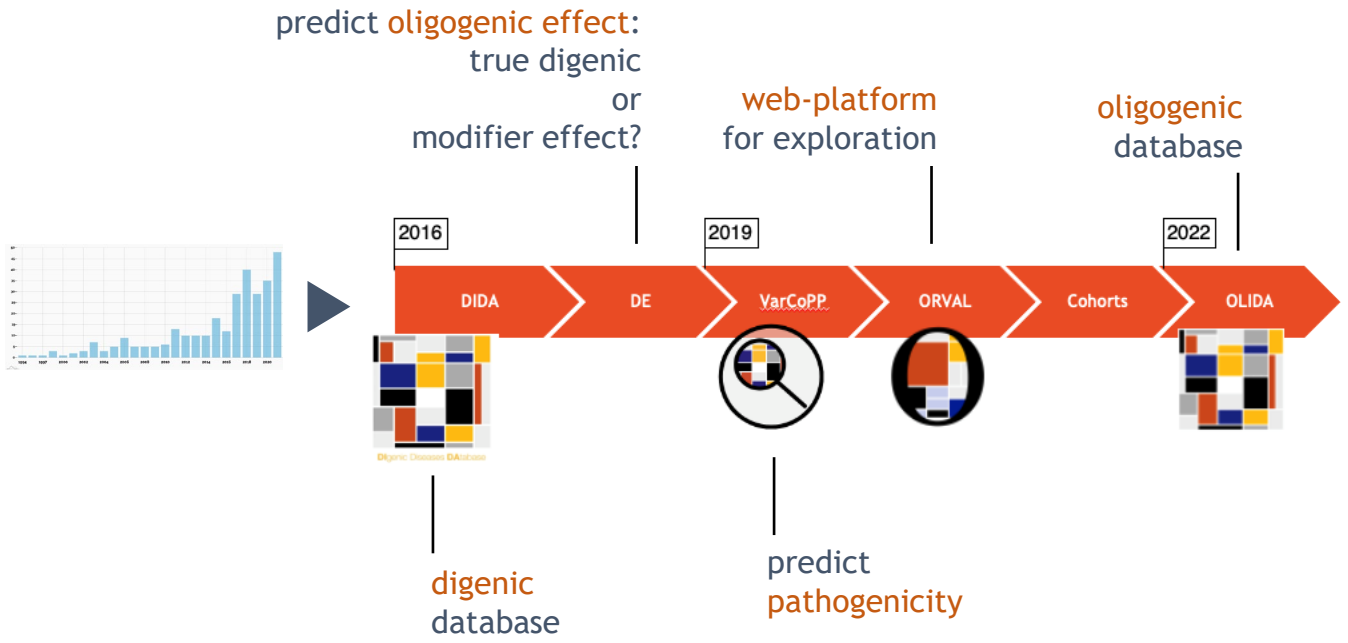



Renaux A., *et al.* (2019). *NAR*. 47 (W1), W93-W98.

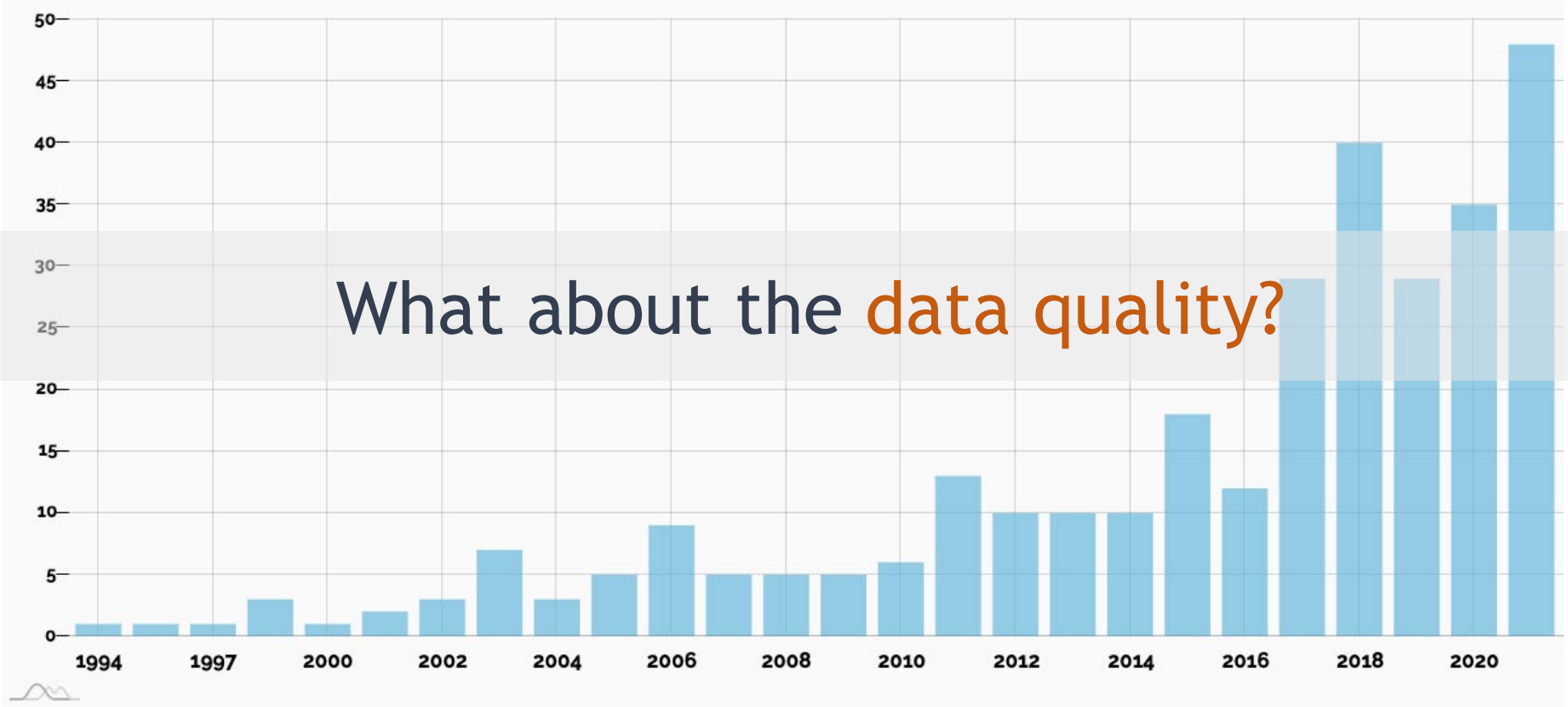
# Developing ML methods for oligogenic diseases



# Developing ML methods for oligogenic diseases



# The data continues to increase




What about the data quality?

Number of publications reporting oligogenic cases

# The data continues to increase


What about the combinations with more genes?

Number of publications reporting oligogenic cases

# OLIDA: the oligogenic diseases database

medical paper

**Data extraction**

2 independent curators: extraction from paper

public knowledge sources


**Evaluation of quality**

**Genetic evidence**

Do the mutations segregate with the disease?

**Functional evidence**

Do functional experiments prove synergistic pathogenicity?

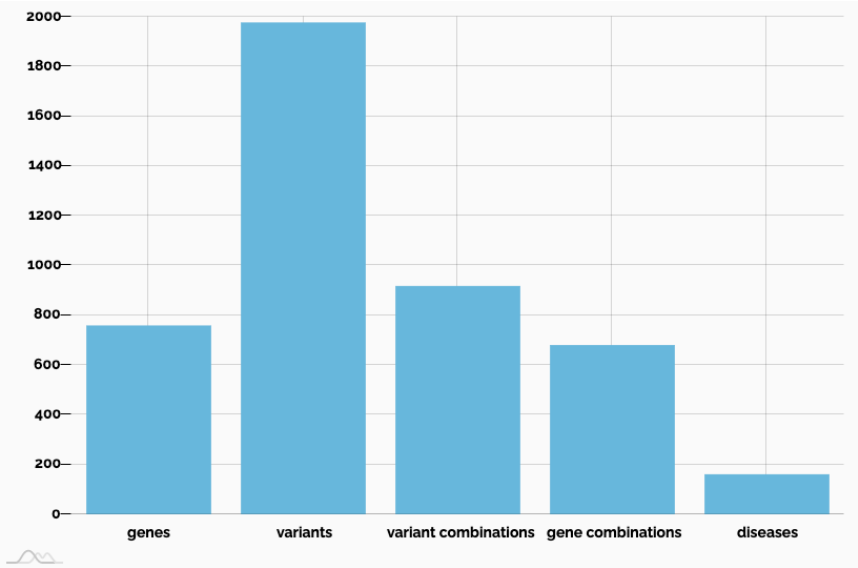
**Confidence score [0 to 3]**

absent, weak, moderate, strong

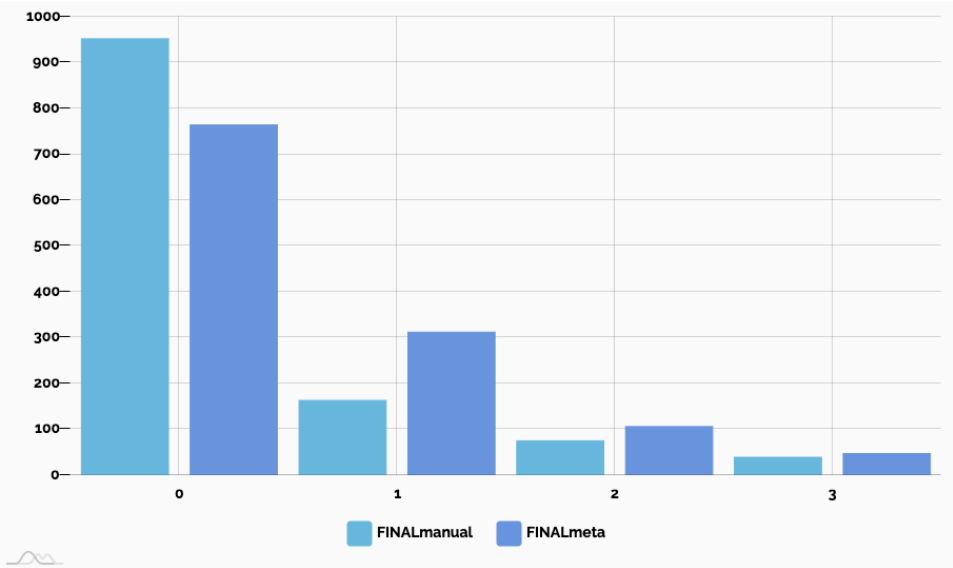
# OLIDA: the oligogenic diseases database

https://olida.ibsquare.be

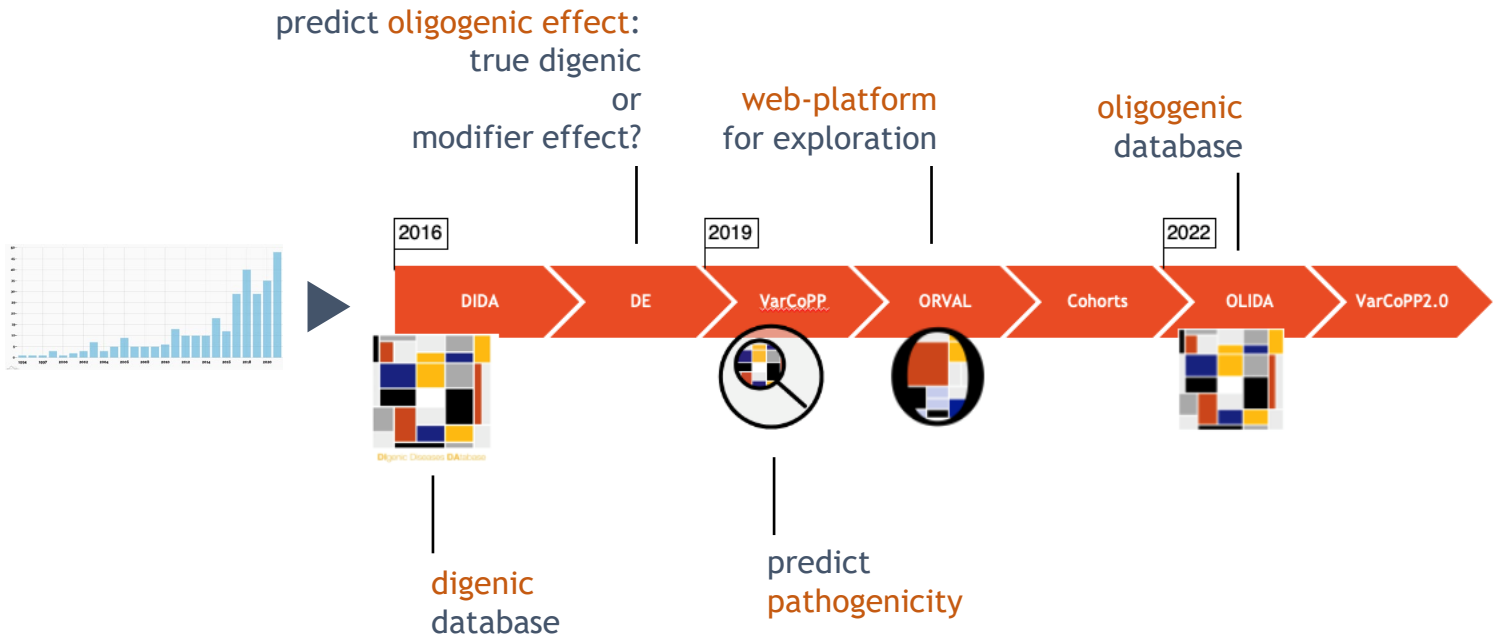
**1,229 oligogenic combinations** linked to **177 diseases**



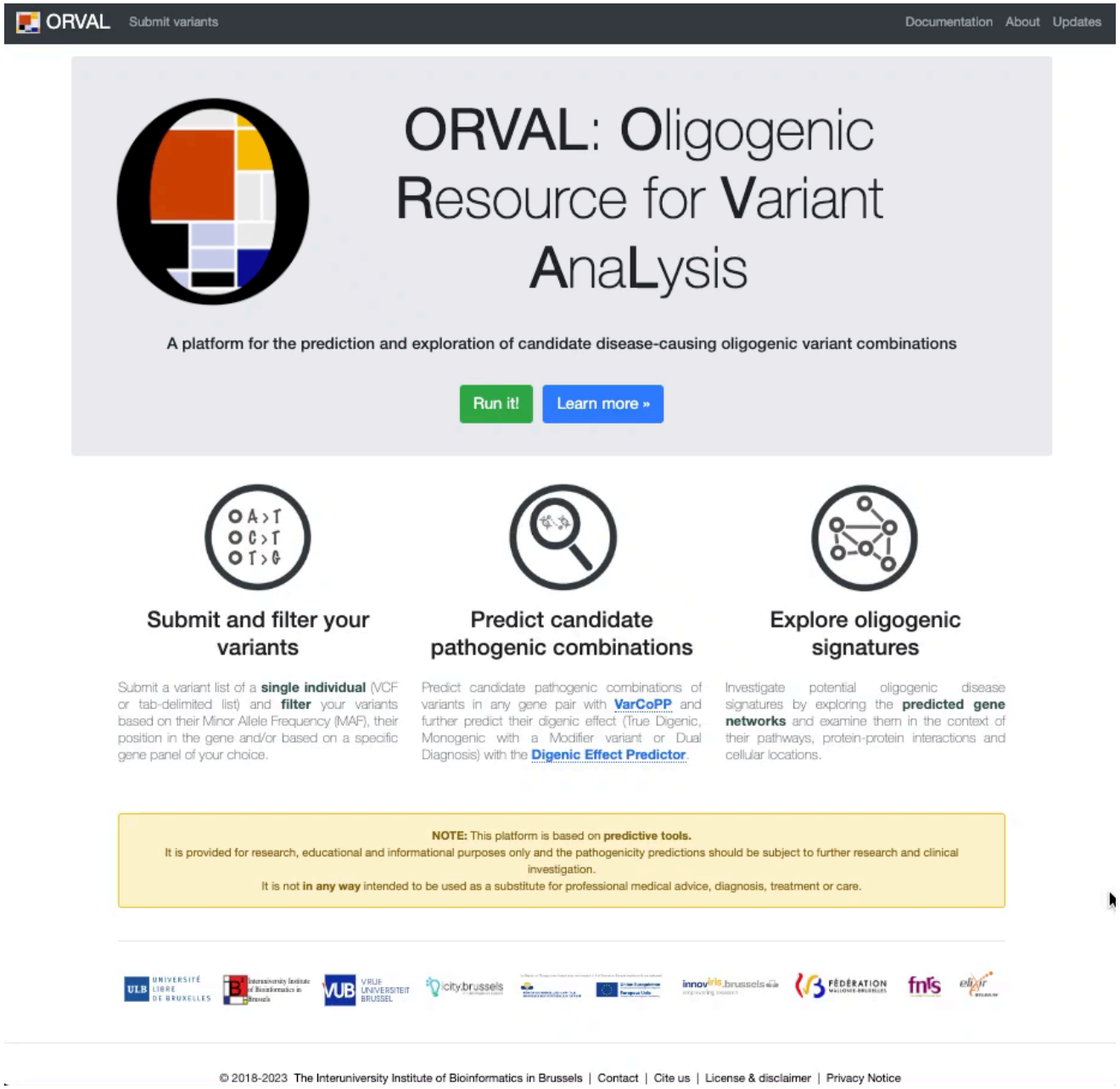

**Be careful of the quality!**



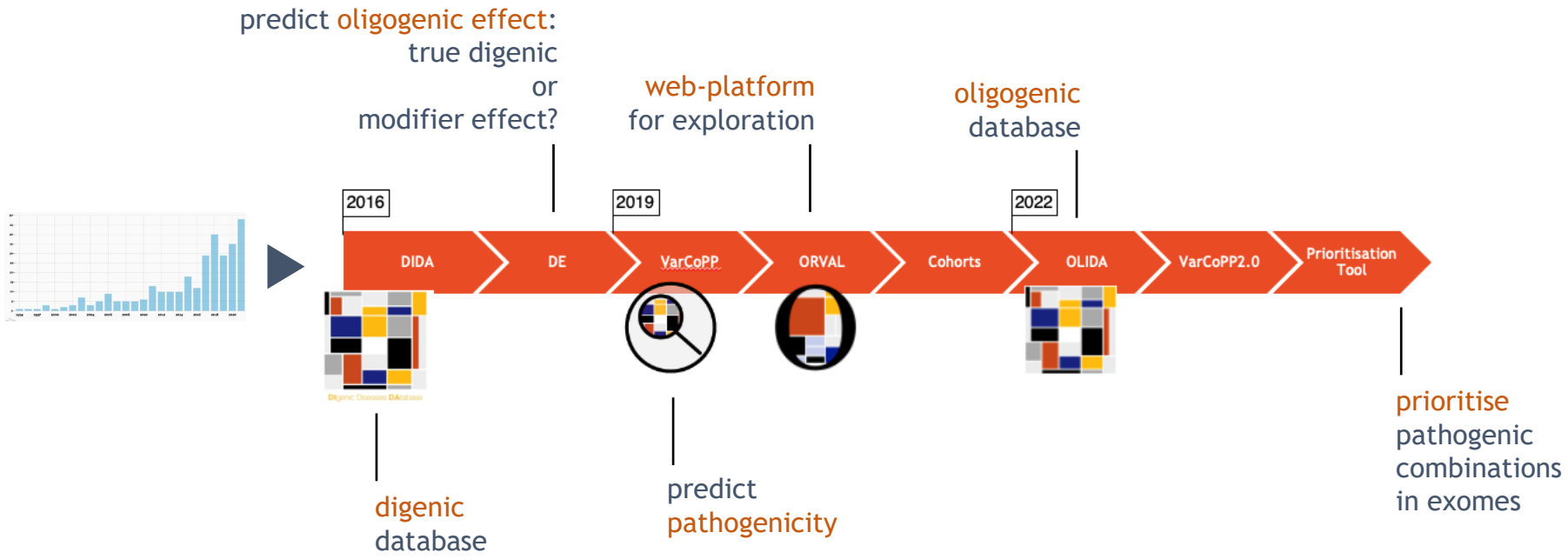
# Developing ML methods for oligogenic diseases



# Demo of ORVAL

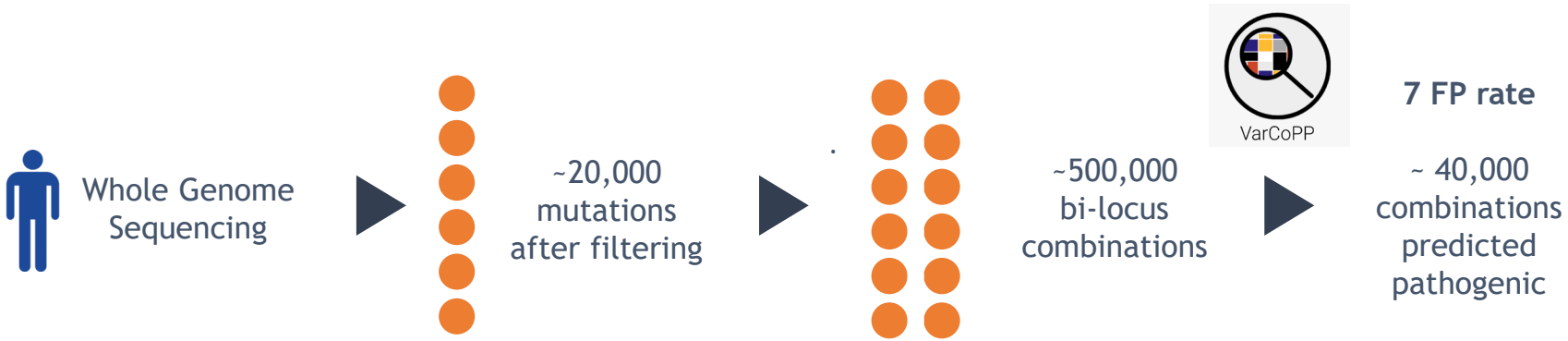


# Developing ML methods for oligogenic diseases



# HOP: prioritizing bilocus combinations

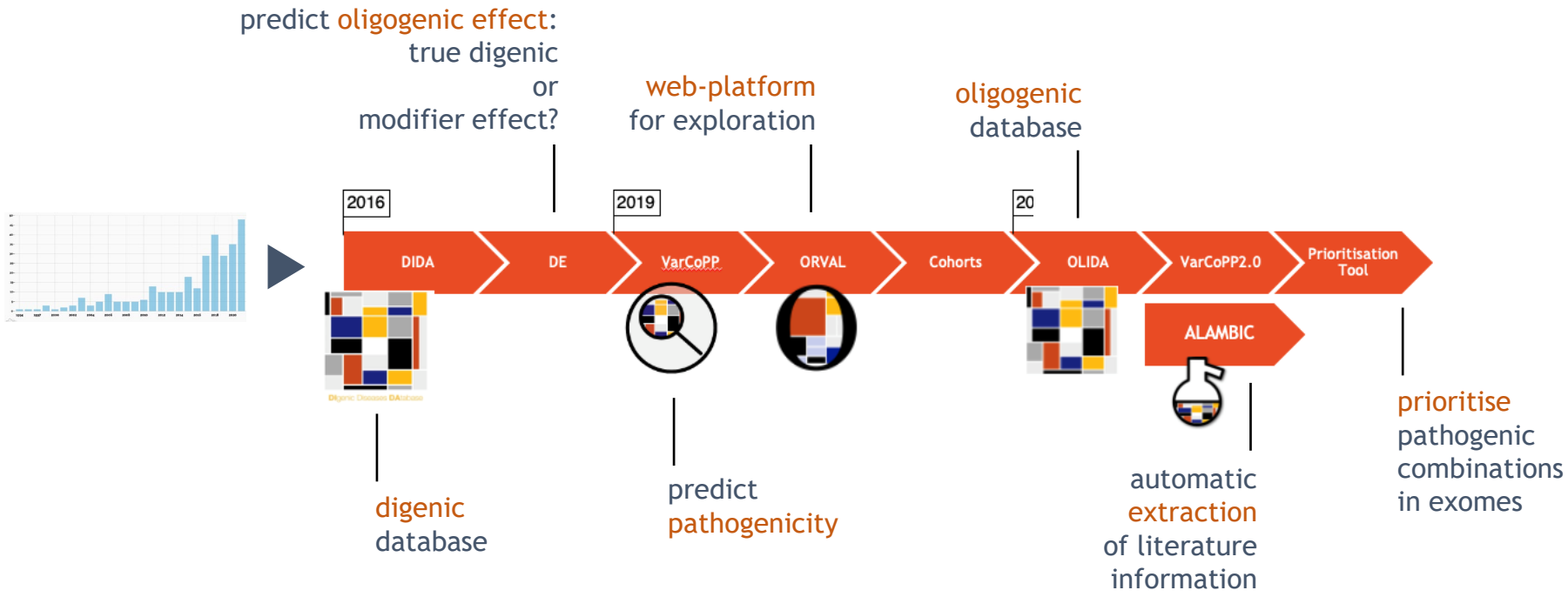
Problem: dealing with too many positive predictions in the whole genome



# HOP: prioritizing bilocus combinations

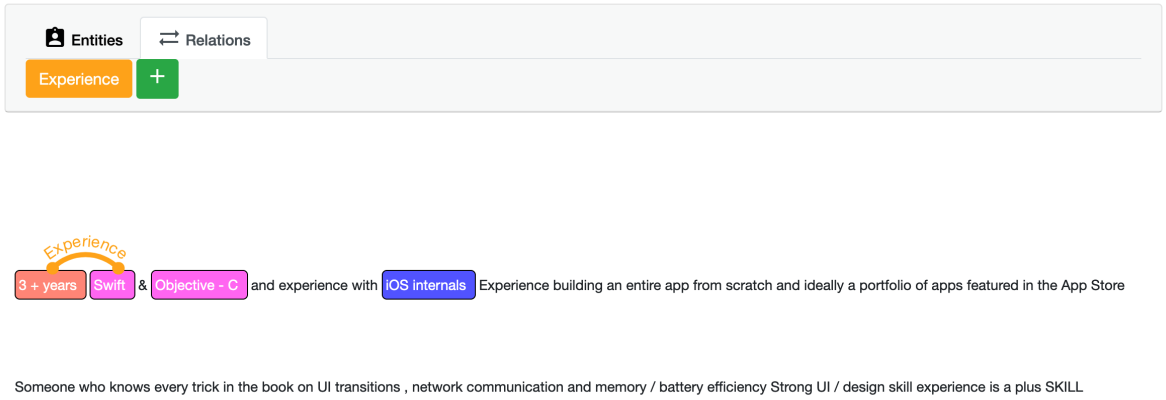
Problem: dealing with too many positive predictions in the whole genome

# Developing ML methods for oligogenic diseases



# ALAMBIC: Active learning for text-mining

**Open-source platform to train models for many types of data, including medical data**




- Handles images and data
- Implements classification, annotations and relation extraction tasks
- Tracks progress and performance
- Download of the trained model, annotated data

# ALAMBIC: Active learning for text-mining

**Open-source platform to train models for many types of data, including medical data**

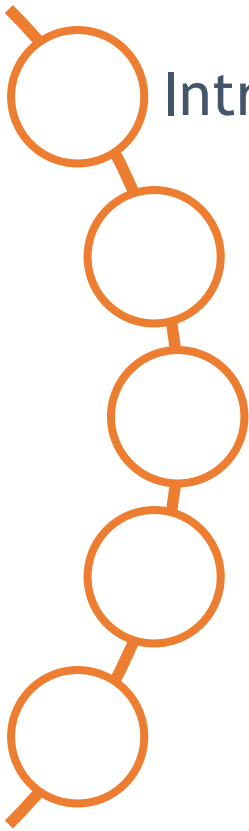
▼

DUVEL: Detection of Unlimited Variant Ensemble in Literature

oligogenic relationship extraction

*We can brew some DUVEL with ALAMBIC*

# Overview



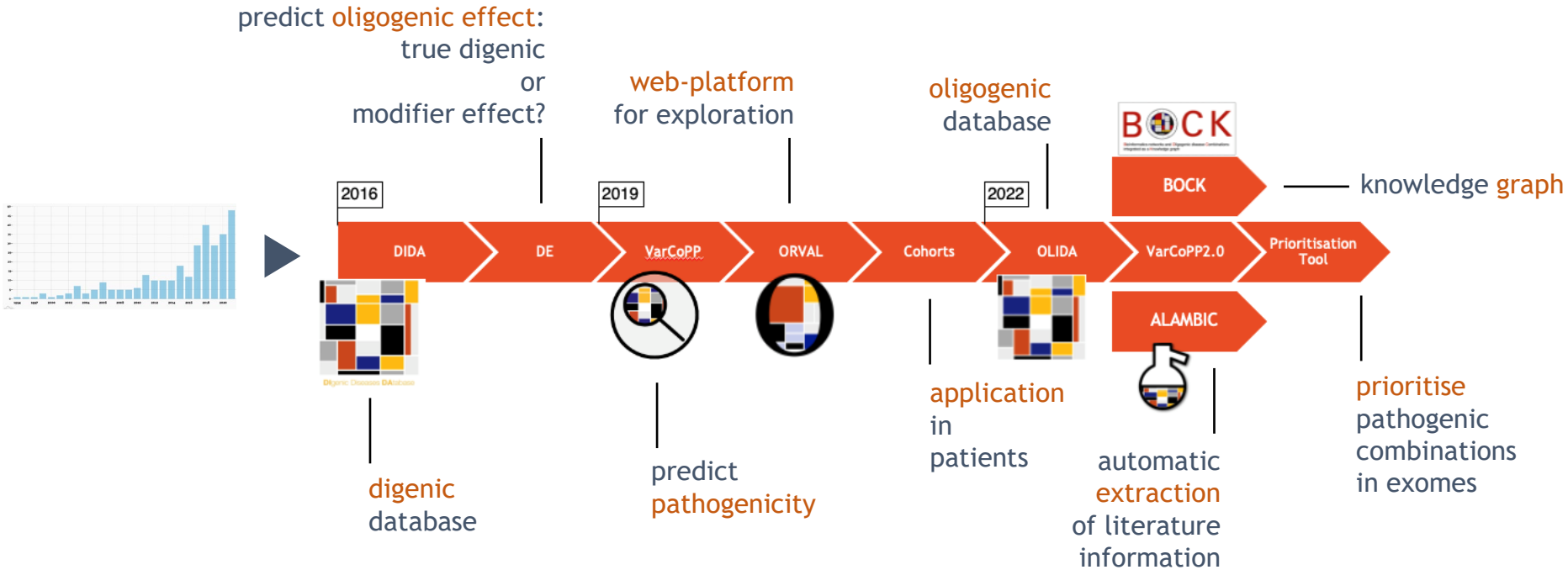
Introduction of the $(IB)^2$

Oligogenic models for missing diagnoses

The data & ML methods for oligogenic diseases

Interpretable ML: transparent diagnoses

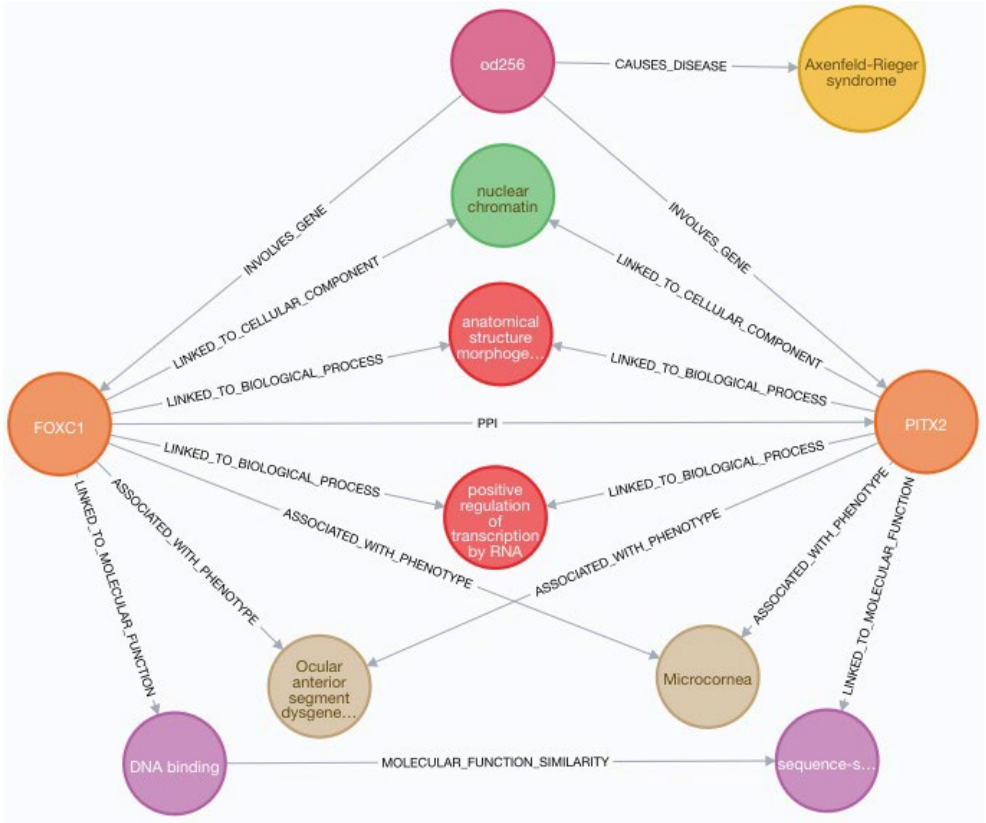
# Developing ML methods for oligogenic diseases



# BOCK: interpreting pathogenic predictions

OLIDA

multilayer knowledge graph

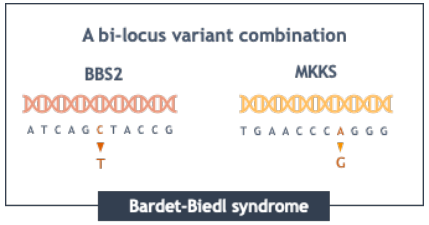



mining of association rules

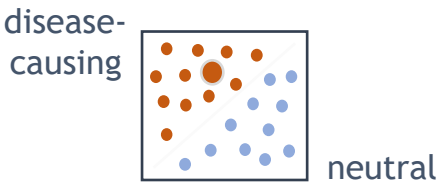
# BOCK: interpreting pathogenic predictions

**White-box proxy model** using **rule—learning** to interpret the **black-box** predictions of VarCoPP

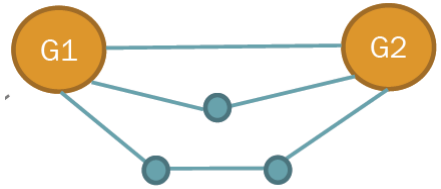
A bi-locus combination of interest



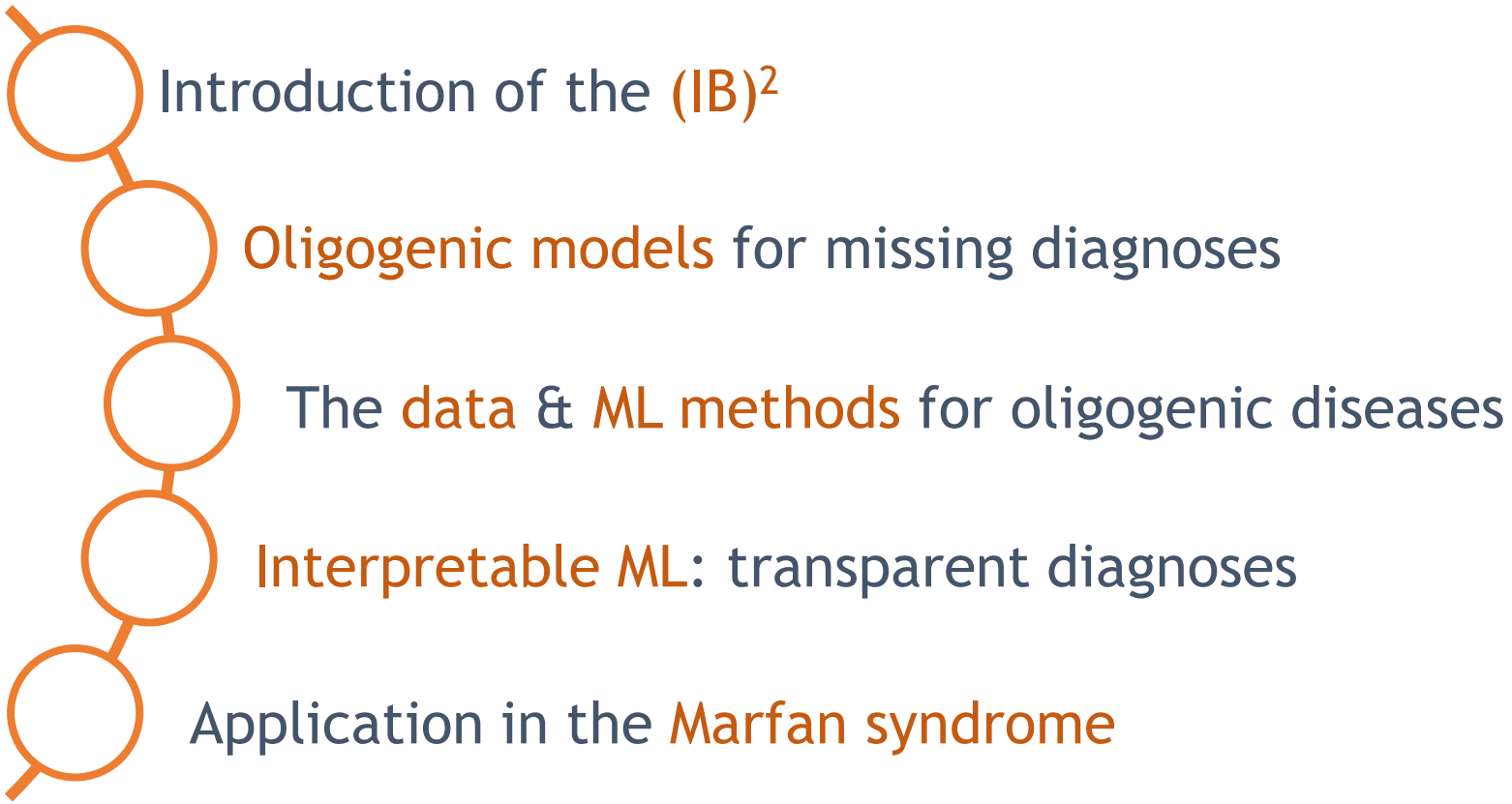

Knowledge discovery with VarCoPP / ORVAL




Interpretation with BOCK



# Overview


Introduction of the (IB)²
Oligogenic models for missing diagnoses
The data & ML methods for oligogenic diseases
Interpretable ML: transparent diagnoses
Application in the Marfan syndrome

# Find oligogenic signatures in Marfan patients

**Genome4Brussels**
Detecting genetic modifiers for Marfan syndrome



Transfer of ORVAL on F101G infrastructure

Development of research platforms for transparent AI and ML for rare diseases

# Find oligogenic signatures in Marfan patients

## The data

Bart Loeys
Antwerp University

101 Genomes Foundation
Genomics for Rare Diseases

Catherine Boileau
Paris Diderot University
University

## The methods

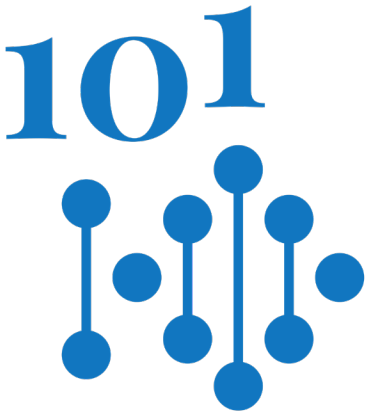
VarCoPPv2, BOCK, network analysis, statistical analysis

## The aim

Detect modifier genes in Marfan patients that can explain their phenotype

# Thank you


icity.brussels
THE ICT HEART OF EUROPE
La Région et l'Europe investissent dans votre avenir ! • Het Gewest en Europa investeren in uw toekomst!
RÉGION DE BRUXELLES-CAPITALE
BRUSSELS HOOFDSTEDELIJK GEWEST
Union Européenne
Fonds Européen de Développement Régional
Europese Unie
Europees Fonds voor Regionale Ontwikkeling
101 Genomes
Foundation
Genomics for
Rare Diseases
funded by
innoviris
.brussels
fnrs
LA LIBERTÉ DE CHERCHER
elixir
BELGIUM
TRAIL
FÉDÉRATION
WALLONIE-BRUXELLES
ULB
UNIVERSITÉ
LIBRE
DE BRUXELLES

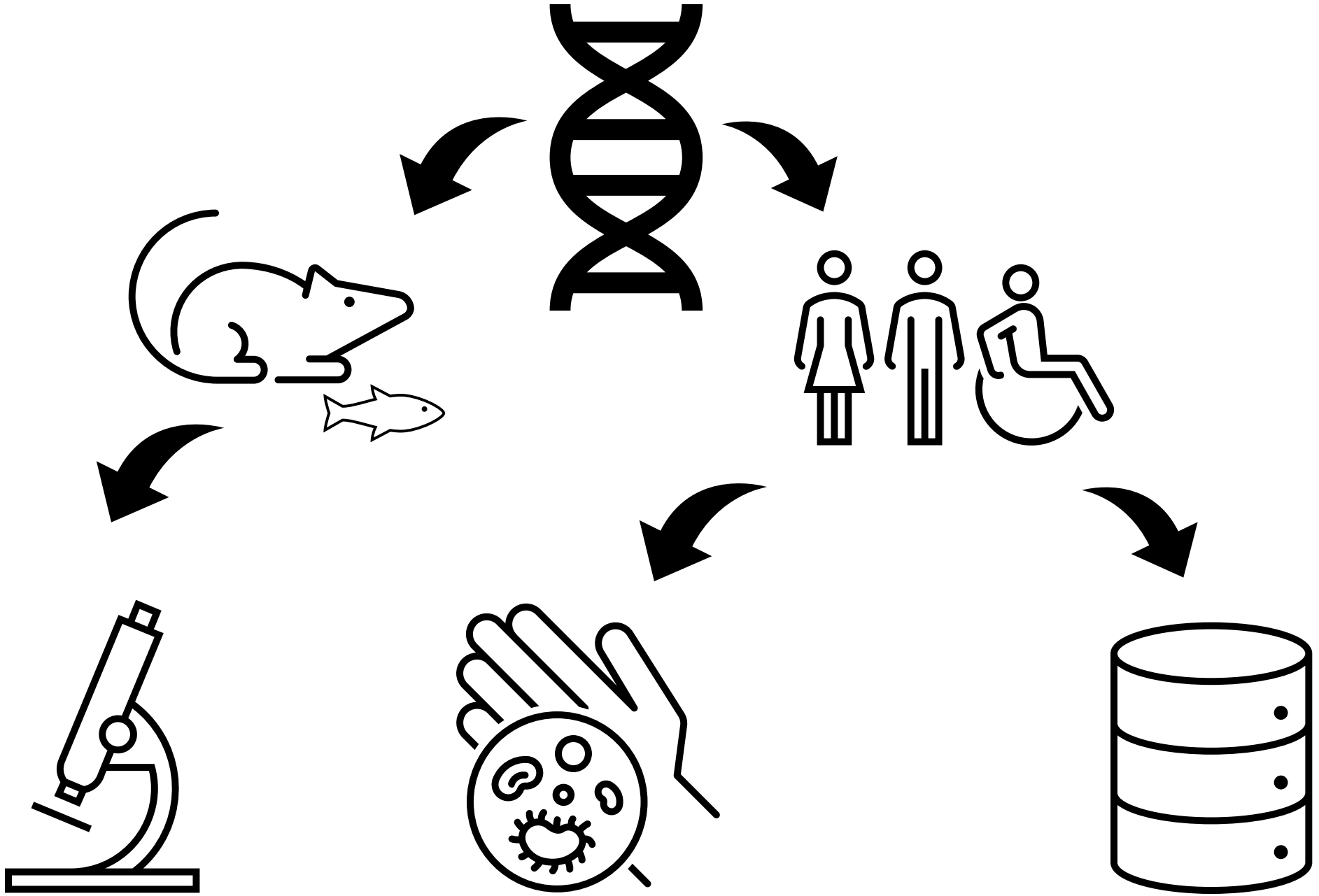



***Note: in silico***

**Done with Marie Glanc, AssoMarfans**

**2017: 1**
**2021: 3**
**2022: 10**

| Titre | Date publicatio | nom gène | loci impac | 1er auteur |
|---|---|---|---|---|
| No prominent role for complement C1-esterase inhibitor in Marfan syndrome mice | 30/10/2022 | IL11 | poumon | Ng B. |
| DNA methylation alternation in Stanford- A acute aortic dissection | 29/10/2022 | Fas, ANGPT2, DUSP6, FARP1, CARD6 | aorte | Chen Y. |
| Embryologic origin influences smooth muscle cell phenotype modulation signatures in Marfan syndrome aortic aneurysm | 24/10/2022 | C1R | aorte | Hibender S. |
| Il11 Causes Pulmonary Tissue Remodeling and Emphysematous Lung Disease in the Fbn1C1041G/+ Mouse Model of Marfan Syndrome | 01/09/2022 | TWIST1 | aorte | Pedroza A. J. |
| Inhibition of HIPK2 Alleviates Thoracic Aortic Disease in Mice With Progressively Severe Marfan Syndrome | 01/06/2022 | CNP | aorte | Clerc S. |
| Novel Effector Molecules Regulating Smooth Muscle Cell Contractility in Marfan Syndrome: Phosphoprotein 1 Secreted by Fibroblasts | 23/05/2022 | Mir-122 | aorte | Zhang R.-M. |
| The C-type Natriuretic Peptide: a new player in the development of the Marfan syndrome? | 17/05/2022 | SPP1 | aorte | Chen R. |
| A phenotypic screen of Marfan syndrome iPSC-derived vascular smooth muscle cells uncovers GSK3β as a new target | 12/04/2022 | GSK3β | aorte | Davaapil H. |
| Aortic Dilatation in Marfan Syndrome: A Result of Amplification of Molecular Mechanisms of Aging? | 15/02/2022 | NOTCH3 | aorte | Jespersen K. |
| Impact of Notch3 Activation on Aortic Aneurysm Development in Marfan Syndrome | 01/02/2022 | TTN, POMT1 | aorte | Min-Rou L. |
| Application of Whole Exome Sequencing and Functional Annotations to Identify Genetic Variants Associated with Marfan Syndrome | 02/10/2021 | PRKG1 | aorte | Toral M. |
| Extracellular Tuning of Mitochondrial Respiration Leads to Aortic Aneurysm | 21/09/2021 | HIPK2 | aorte | Caescu C. I. |
| The NO signalling pathway in aortic aneurysm and dissection | 25/05/2021 | TFAM | aorte | Oller J. |
| Fibrillin-1-regulated miR-122 has a critical role in thoracic aortic aneurysm formation | 01/05/2017 | RUNX2 | aorte | Hagler M. A. |



# PART 3
# Consent, access and interactions

# GDPR & patients rights

**Me Thomas DUBUISSON**

CMS DeBacker
Avocats-Advocaten

Chaussée de La Hulpe 178
1170 Brussels
Belgium

T +32 2 743 69 00
F +32 2 743 69 01

www.cms.law

Thomas Dubuisson
E thomas.dubuisson@cms-db.com

For the attention of:

Member of the Ethics Committee

15 September 2022

Your ref. :
Our ref. : 60270 - Fondation 101 Génomes (**F101G**)

## A. OVERVIEW

1. The Regulation (EU) 2016/679 (**GDPR**) applies directly to Belgium that enacted: (i) the Act of 3 December 2017 on the creation of the Belgian Data Protection Authority (**BDPA**). The BDPA enforces sanctions for non-compliance with the GDPR; and (ii) the Belgian Data Protection Act of 30 July 2018 (**Belgian Privacy Act**), which aligns Belgian data protection law with the GDPR. The GDPR and the Belgian Privacy Act apply to the processing of personal data wholly or partly by automated means and to the processing other than by automated means of personal data which form part of a filing system or are intended to form part of a filing system.

2. Belgium has also adopted specific legislations for certain cases, such as, the: Law of 22 August 2002 on the patient rights that regulates, among other things, the use of patients' data and the information that patients need to receive in respect of this use and the Law of 21 August 2008 on the institution and organization of the eHealth platform and laying down various provision

3. Broadly speaking, there are 2 tiers of **administrative fines** for non-compliance with the Belgian Privacy Act and GDPR. Fines are discretionary rather than mandatory and are imposed on a case-by-case basis and should be effective, proportionate, and dissuasive (see Art. 83, GDPR and Court of Appeal Brussels (Market Court section), Judgment 2020/1471 of 19 February 2020):

   - The first is up to EUR 10 million or 2% of annual global turnover of the previous year, whichever is higher (for infringements of articles: 11 (processing that doesn't require identification); 25 – 39 (general obligations of processors and controllers) (**Tier 1 fines**); and
   - The second is up to EUR 20 million or 4% of annual turnover of the previous year, whichever is higher (can be issued for infringements of articles: 5 (data processing principles); 6 (lawfulness of processing); 7 (conditions for consent); 9 (processing of special categories of data); 12 – 22 (data subjects' rights); and 44 – 49 (data transfers to third countries or international organizations) (**Tier 2 fines**).

   In addition to the administrative fines provided for in the GDPR, the Belgian Privacy Act (see articles 222 to 230) also introduces different tiers of **criminal penalties** for violations of the Privacy Act (as well as the GDPR itself), with a maximum penalty of EUR 30,000 (considering the mandatory multiplication of criminal fines, this equals a *de facto* maximum fine of EUR 240,000). The Privacy Act also clarifies that a controller and/or processor is in principle **civilly liable** for the payment of the fines which have been imposed on his contractor or agent. Any person (such as employee) who suffers material or non-material damage from an infringement of the GDPR may receive compensation from the controller for the damage suffered (e.g. by non-compliant processing).

4. The BDPA recalled early this year that "*the GDPR entered into force in 2016 and became applicable on 25 May 2018. In the meantime, almost 4 years have passed since the GDPR became applicable, a period that has not been sufficiently used by* [the company] *to make its operation GDPR-compliant*" (BDPA, Litigation Chamber, Decision on the merits 45/2022, 30 March 2022).

## B. F101G : GDPR COMPLIANCE ASSESSMENT

5. Data protection is based on activities (e.g. steering, record of processing activities, legal monitoring) implemented by each organization, such as F101G.

6. F101G has instructed CMS to reach into compliance. Based on this mandate, CMS drafted several documents related to the GDPR such as policies and consent forms. As a result, we are of the opinion that F101G has taken various and adequate measures to comply with the GDPR. The measures taken included, amongst others:

   - **Record of processing activities (ROPA)**. F101G has drafted a ROPA which allows a company (in this case, F101G) to make an inventory of all the data processing activities and have an overview of what it is doing with the concerned personal data.
   - **Privacy statements**. F101G has drafted an external facing privacy policy, optimal in terms of user centricity and engagement factors. It is reachable on the website in 3 languages (French, Dutch, and English). It is in (i) clear and plain language, concise and intelligible; (ii) easily accessible for the data subjects; (iii) comprehensible i.e. data subjects have a fair understanding of what they can expect with regards to the processing of their personal data. F101G also has a separate cookie policy on its website.
   - **Consent forms**. F101G has drafted various consent forms to collect the personal data in accordance with the GDPR and related Belgian specific legislations.
   - **Third Party agreements - Data Processing Agreements (DPAs)**. F101G has entered into various contracts (DPA) with third party ensuing that all parties involved are properly handling personal data and that they comply with the GDPR's requirements.
   - **Data transfers**. F101G has reviewed the personal data flows to identify potential cross-border transfers. The personal data processed by F101G is not transferred outside the European Economic Area (EEA). F101G is also monitoring supervisory authority guidance on cross-border transfers.
   - **Cybersecurity**. When processing personal data, F101G considers, at the outset, the privacy impact of any systems it adopts, develops, or commissions, which may process personal data. In particular, F101G ensures that such systems include: (i) appropriate technical and organisational measures, to achieve data protection principles (such as data minimisation) in an effective manner and (ii) necessary safeguards to meet the requirements of the GDPR and protect the rights of data subjects.
   - **Compliance program**. F101G has implemented a GDPR compliance program with CMS that is continuously maintained to avoid, or at least minimise, potential liability. Having a formal compliance program in place will enable to demonstrate commitment to data protection compliance if it is called into question by regulators (BDPA) or courts.

7. GDPR compliance is not a box-ticking exercise. It is important to implement a review cycle to detect changes, deviations, and perform corrective actions when required to ensure sustainability. F101G will continue to review its processing activities to ensure that they enable continuous compliance with GDPR principles and will allow it to fulfil its obligations in this respect.

8. Based on the above, we are of the opinion that the actions carried out by F101G are in accordance with a defined (e.g. use of methods), standardised (common to the whole company) and formalised (existence of documentation) process. The people carrying out the actions have the appropriate skills for the process. F101G supports the process (it provides the resources and means necessary for its operation). The process is also well understood by both management and employees. As a result, F101G will be able to demonstrate compliance with data protection rules.

***

I remain at your disposal for any questions you may have.

Yours faithfully,

Thomas Dubuisson

F101G has instructed CMS to reach into compliance. Based on this mandate, CMS drafted several documents related to the GDPR such as policies and consent forms. As a result, we are of the opinion that F101G has taken various and adequate measures to comply with the GDPR. The measures taken included, amongst others:

- **Record of processing activities** (**ROPA**). F101G has drafted a ROPA which allows a company (in this case, F101G) to make an inventory of all the data processing activities and have an overview of what it is doing with the concerned personal data.

- **Privacy statements**. F101G has drafted an external facing privacy policy, optimal in terms of user centricity and engagement factors. It is reachable on the website in 3 languages (French, Dutch, and English). It is in (i) clear and plain language, concise and intelligible; (ii) easily accessible for the data subjects; (iii) comprehensible i.e. data subjects have a fair understanding of what they can expect with regards to the processing of their personal data. F101G also has a separate cookie policy on its website.

- **Consent forms**. F101G has drafted various consent forms to collect the personal data in accordance with the GDPR and related Belgian specific legislations.

- **Third Party agreements - Data Processing Agreements (DPAs)**. F101G has entered into various contracts (DPA) with third party ensuing that all parties involved are properly handling personal data and that they comply with the GDPR's requirements.

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[Privacy Policy - 101 Genomes Foundation (f101g.org)]

101 Genomes Foundation
Genomics for Rare Diseases

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PRIVACY POLICY
COOKIE POLICY

# Privacy Policy

*November 15, 2022 version*

**Content**



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**BIC: BPOTBEB1**
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PRIVACY POLICY
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# Cookie Policy

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This Cookie Policy explains what cookies are and how we use them, the types of cookies we use i.e., the information we collect using cookies and how that information is used, and how to control the cookie preferences. For further information on how we use, store, and keep your personal data secure, see our Privacy Policy.

You can at any time change or withdraw your consent from the Cookie Declaration on our website
Learn more about who we are, how you can contact us, and how we process personal data in our Privacy Policy.
Your consent applies to the following domains: www.f101g.org

Your current status: Consent accepted. Manage your consent.

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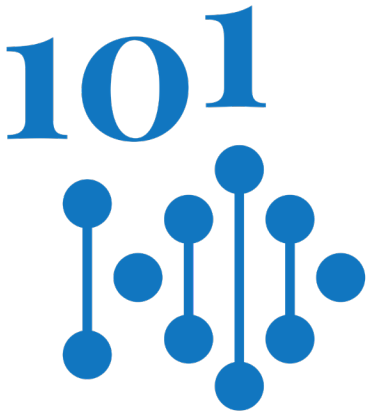
# Profile Management

## Privacy Management Dashboard

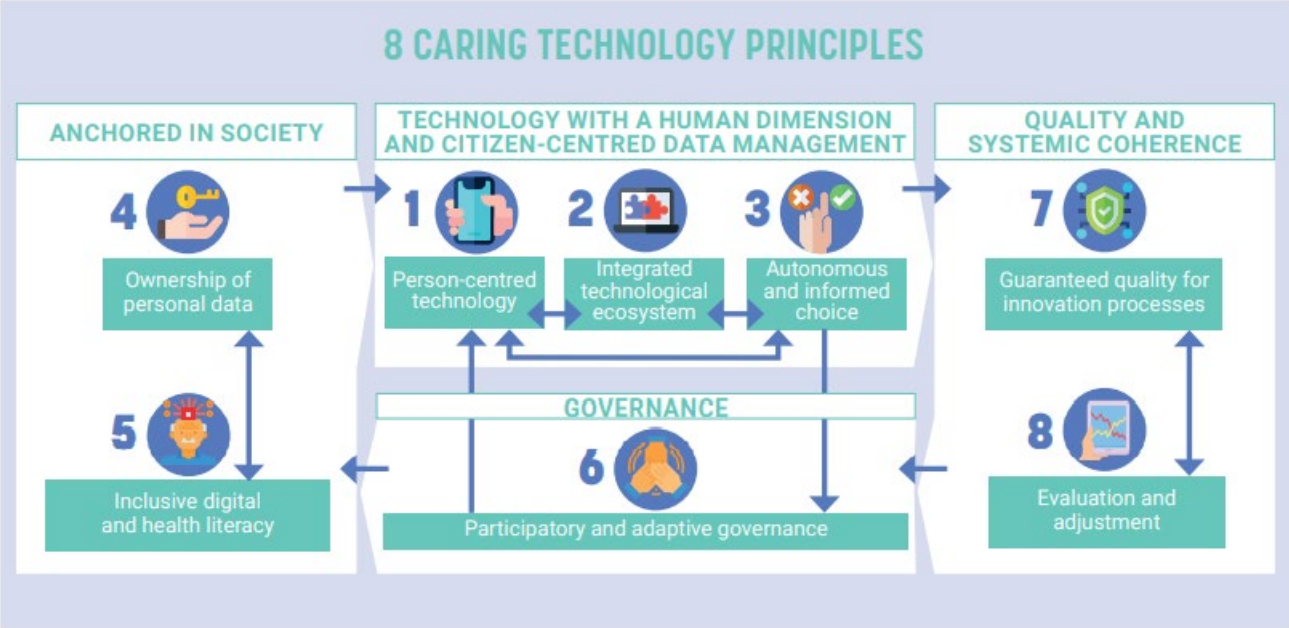



# Data Access

# F101G Data Access
# Guiding Principles

# Eight guiding principles

**FRB | Dr. Daniël De Coninck Fund**




Renforcer la première ligne

FONDS DR. DANIËL DE CONINCK

## The eight guiding principles identified by the King Baudouin Foundation and the Dr Daniël De Coninck Fund

2020 / SATURDAY, JANUARY 2ND, 2021

In October 2020, the King Baudouin Foundation and the Dr Daniël De Coninck Fund communicated the list of eight ethical principles, the "...". **8 Caring Technology Principles** These are the "challenges" that technological innovations in health and wellness must address today and in the future.

Prior to the official publication of these principles, **the King Baudouin Foundation invited the representatives of Fondation 101 Génomes to present and discuss them together during the summer of 2020**.

As a result of this meeting, it emerged that these eight principles are **compatible with the work of the 101 Genomes Foundation and provide a welcome frame of reference.** on which the work of the 101 Genomes Foundation can continue to be built.

# Principles 1 to 3

**Human technology and data in the service of the citizen [P1/P2/P3]**

**PROMOTE HUMANE TECHNOLOGY AND CITIZEN-CENTRED DATA MANAGEMENT**

**1** Ensure that the role of technology and use of data always facilitate and support people and that they remain at the service of people and society. Maximise opportunities for citizens to make their own decisions based on their care needs, support requirements and health-related wishes.

**2** Encourage ongoing collaboration among all the actors involved, through the creation of an integrated technological ecosystem in which interoperability, standardised protocols and open-source (basic) technology are all self-evident. Support patients and citizens to allow them to participate optimally in the development and adoption of this ecosystem.

**3** Provide honest, reliable, transparent and easily understandable information about innovations in care and health. Make sure people are able to make choices in a truly informed and independent way (true consent) by objectively representing the usefulness, scope, pros and cons of innovations so that people can have confidence in the products they choose.

**Implementation F101G**

Re-contact and multiple consents

WGS, 30x, Illumina & Data *Fairification*

Module and involvement genetic counselor

# Principles 4 to 6

**Societal anchoring and governance [P4/P5/P6]**

**ANCHORED IN SOCIETY**

**4** Improve trust between people and organisations in regard to the use of data and data-driven innovations, by allowing them to have ownership of their own data. Support citizens to share these data safely and use it to leverage their own personal well-being and promote the public interest.

**5** Promote technological literacy, health skills and participation among all citizens. Make lifelong learning for all a goal. Ensure that no-one is left behind, including vulnerable and underprivileged people and those needing special attention. Innovation should be focused on reducing both the digital gap and the health gap rather than further widening them.

**STIMULATE PARTICIPATORY GOVERNANCE**

**6** Develop participative and adaptive governance for the innovation system. Encourage citizens and stakeholders to participate actively in this. Make flexible but effective adjustments to policy on the basis of new data, experience, evidence and growing expertise.

**Implementation F101G**

Excluding deductibility of developable property

F101G funds WGS for the most vulnerable

DAC, *Fair Genomics*, DPO, Supervisory Committee

# Principles 7 and 8

**Quality & consistency [P7/P8]**

## CONTROL QUALITY AND SYSTEMIC COHERENCE

**7** Develop quality assurance systems for the whole innovation trajectory, i.e. cover the periods before, during and after the development and deployment of technology and the use of data. There must be controls on the content, safety, transparency of information, and on its traceability, usefulness and effectiveness. Knowledge gained through experience must have a place alongside scientific evidence. Introduce quality labels to communicate the results of these controls and assessments.

**Implementation F101G**
Quality and Control Audit Group

**8** Monitor and evaluate to ensure that the actions taken remain coherent with health and care goals within wider frameworks of prevention, ethics and sustainability. Integrate sustainability objectives and appropriate ethical principles (e.g. human rights) in the innovation growth pathway.

**Implementation F101G**
Oversight Committee, Annual Access Report

# F101G Data Access Process

# What kind of access are we talking about?

**Consultation *in the Cloud***

- The data collected is **processed under the control of** the F101G to **be accessible in electronic format in the Cloud**.
- **The datasets collected by the F101G do not leave the instance where they are stored in the cloud**.
- Authorized groups can access datasets in the cloud and install the bioinformatics tools they need to conduct their analyses, but they cannot retrieve or save them locally. **Only research results are repatriated and belong to the researchers**.

# Who has access to genomes?

**Researchers, physicians & genetic analysis specialists**

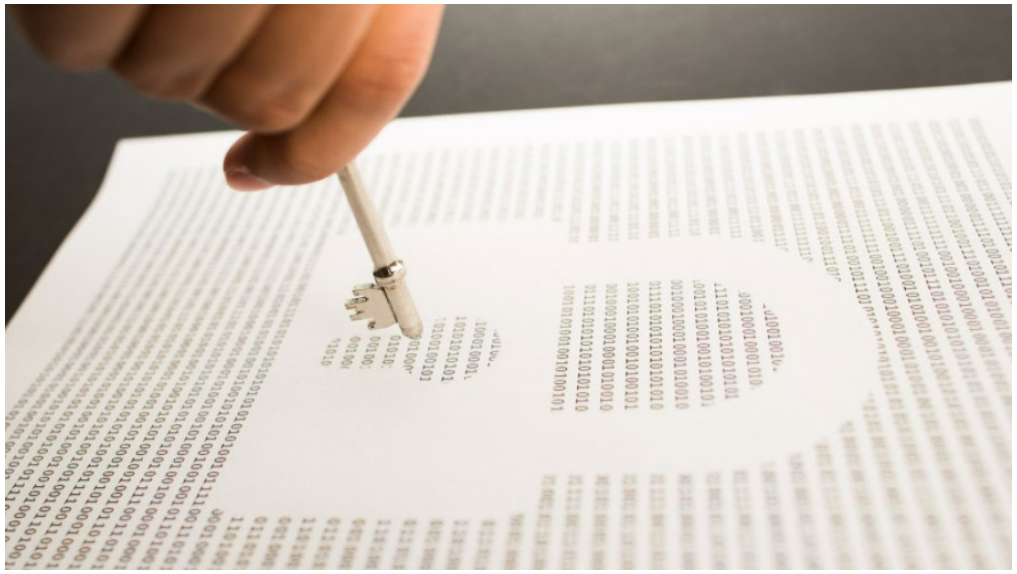
The data collected can be accessible to:

- academic / industrial **research groups** and
- in specific cases, to the **participant's physician**

# Who authorizes access?

## Data Access Committee (DAC) [P6]

- All access requests are directed to the **Data *Access* Committee** (DAC) of the F101G.
- This DAC is composed of (1) representatives of the **F101G** (including its Data Protection Officer (**DPO**)), (2) **representatives of patient associations**, (3) **scientists**, and (4) a **specialist in ethical issues**.
- The DAC verifies the **scientific and ethical legitimacy of access requests** and provides an opinion on access requests according to the **guidelines** issued by the F101G.
- The composition and operation of the DAC of the F101G will be governed by specific internal rules of procedure (IOR).



# How is the access formalized?

## F101G and DPO [P6]

- Once authorization has been granted by the DAC, **F101G will formalize access via access agreements**.
- These agreements shall  address issues such as **operational and administrative costs specific to the provision of access.**
- The access agreements address other specific issues depending on the source and scope of the access requests.
- Access authorizations granted by the DAC and formalized in **access agreements are submitted to the Data Protection Officer (DPO)** of the F101G before signature.

Délégué à la protection des données

Reminder: F101G will bear the costs of sequencing and data storage but not the costs of access and analysis. In any event, all costs associated with access and analysis will be borne by the access requesters in accordance with the access agreement.

# Principle: access to aggregated data

**Anonymized data from all participants (or a specific group) [P1/P3].**

- **Access request from an academic research group**
  - The Access Agreement provides for, among other things:
    - communication of results and mention in subsequent publications.
- **Access request from a pharmaceutical/industrial research group** that would, for example, need access to phenotyped genomic data to **validate *in silico* certain proposals for developing new drugs** or **new diagnostic tools**.
  - The Access Agreement provides for, among other things:
    - a commitment to **reasonable pricing** for new products (drugs, treatments, etc.) that could be developed through granted access.
    - a form of support for the **sustainability of the** F101G's **work** (e.g. making phenotyped genomic data available, funding new sequencing, etc.)
- **Whenever an aggregated data access agreement is signed, the information is available to participants**.

# Exception: access to individualized data?

**Hypothesis researcher-initiated [P1/P3]**

- A request from **a researcher who, in the course of conducting research on aggregated data** to which he has previously had access, **would like to specifically contact a particular participant again**, either to obtain **additional individual information or to invite him to join a specific research study**, or **to inform the participant that he has**, by chance during the course of the research, **identified information that is potentially important to the health of that participant.**
  - These access requests are reviewed on an **urgent basis** by the DAC.
  - If the DAC allows this access:
    - either the F101G contacts the participant (1) to solicit **the additional information requested from** him/her and, if the participant agrees, to transmit it to the researcher or (2) to propose that he/she **agrees to join a specific research,**
    - or informs the **participant's physician for him to decide if it is potentially important information for the participant's health** identified and, if necessary, to transmit it within an appropriate ethical framework (see **Charter for health professionals**).

# Who controls quality and safety?

## Quality and Safety Audit [P2/P7]

- A **quality and safety** audit group is commissioned by the F101G
  - To **verify the quality of the** genomic and phenotypic **data** collected
  - **Conduct continuous monitoring of the security level of data storage**
  - To ensure that **no group** authorized to access data hosted by the F101G **exceeds** (intentionally or unintentionally) **the scope of access granted to them**,

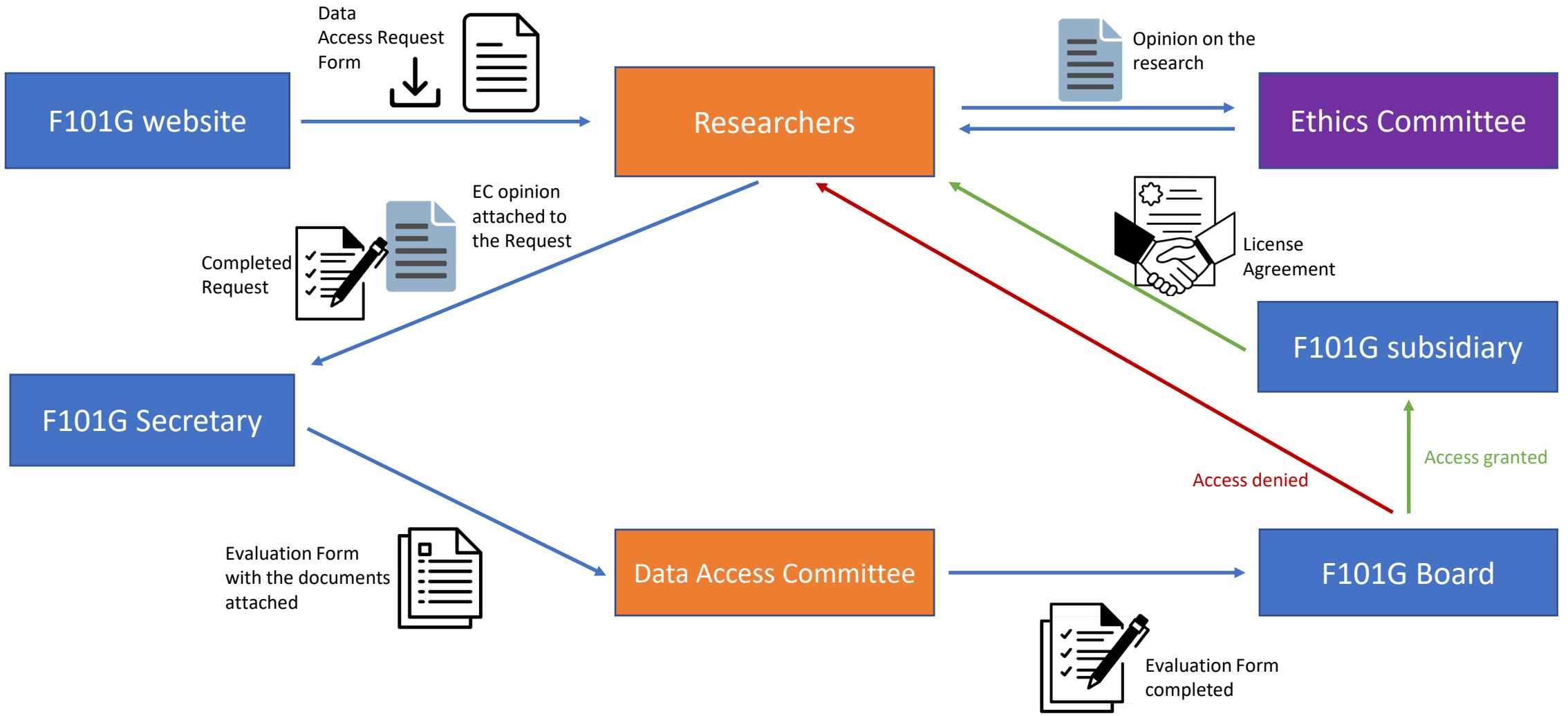
Fondation Roi Baudouin
Agir ensemble pour une société meilleure

# Who monitors systemic consistency?

## Monitoring: Supervisory Committee [P8]

- The access procedure therefore involves the **Data** Access Committee (DAC) of the F101G (composed of representatives of patient associations, scientists and a specialist in ethical issues), *fair genomics* (the subsidiary of the F101G), the **Data Protection Officer** (DPO) of the F101G and, if necessary, in some cases, the **donor's referring doctor**.
- Annually, the F101G will provide a full report of access decisions to an independent *Ad Hoc* **Oversight Committee** to evaluate and advise on the process.
- This report and the opinion given **are available to all participants**.

# Data Access Request Process



# Other genomic initiatives

# National or international

# The 100,000 Genomes Project

**100k, 1million, 5 millions**

## Secretary of State for Health and Social Care announces ambition to sequence 5 million genomes within five years

Posted on October 2, 2018 at 5:00 pm

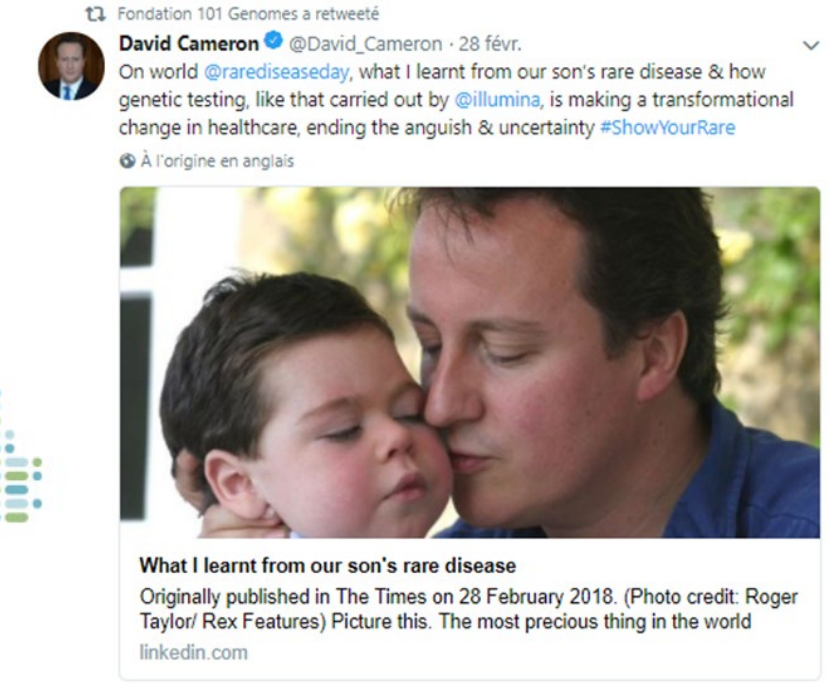
Secretary of State for Health and Social Care, the Rt Hon Matt Hancock MP, today set out an ambitious vision for genomic medicine in the NHS – with plans to sequence 5 million genomes over the next five years.

The announcement, made as part of the Secretary of State's speech to the Conservative Party Conference in Birmingham, recognises the critical importance of genomic medicine to the future of the NHS. Mr Hancock announced:

Health and Social Care Secretary Matt Hancock

- Expansion of the 100,000 Genomes Project to see 1 million whole genomes sequenced by the NHS and UK Biobank in five years.
- That from 2019, the NHS will offer whole genome analysis for all seriously ill children with a suspected genetic disorder, including those with cancer. The NHS will also offer the same for all adults suffering from certain rare diseases or hard to treat cancers.
- Revealed the aspiration to sequence 5 million genomes in the UK, within an unprecedented five-year period.

Genomics england




- The **100,000 Genomes Project in the United Kingdom**.
- The British Secretary of State for Health announced on 2 October 2018 the extension of this Project from 100,000 to **1 million genomes** with
- The ambition to reach **5 million genomes within 5 years.**

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Genomics England

Genomic Medicine | Our Initiatives | Patients and Participants | Research and Partnerships | News and Events | About Us

Overview of GECIP | Join GECIP | Research projects

Cancer +

Cross Cutting +

Rare Disease +

## Cardiovascular

Read about this domain → | Browse all domains →

Order

| Project Title | Project Lead | Project Date |
|---|---|---|
| Phenotyping beyond the aortic root in patients with pathogenetic variants in HTAD genes | Leema Robert | 20/12/2018 |
| GEne specific Missense VAriant Predictor (GEMVAP) | Leema Robert | 20/12/2018 |
| The 101 Genomes Marfan Project (P101GM) | Leema Robert | 20/12/2018 |
| Genome-wide Epistasis for cardiovascular severity in Marfan Study GEMS | Leema Robert | 20/12/2018 |

To identify the following questions 1. the frequency of some common FBN1 variants such as p.Ile2585Thr in the 100k population 2. depper phenotype of these patients where possible in collaboration with respective GMCs

https://www.genomicsengland.co.uk/research/academic/research-projects?page=1&p-term=Leema%20Robert&p-category=rare-disease&p-domain=cardiovascular&p-order=

# European ‘1+ Million Genomes’ initiative

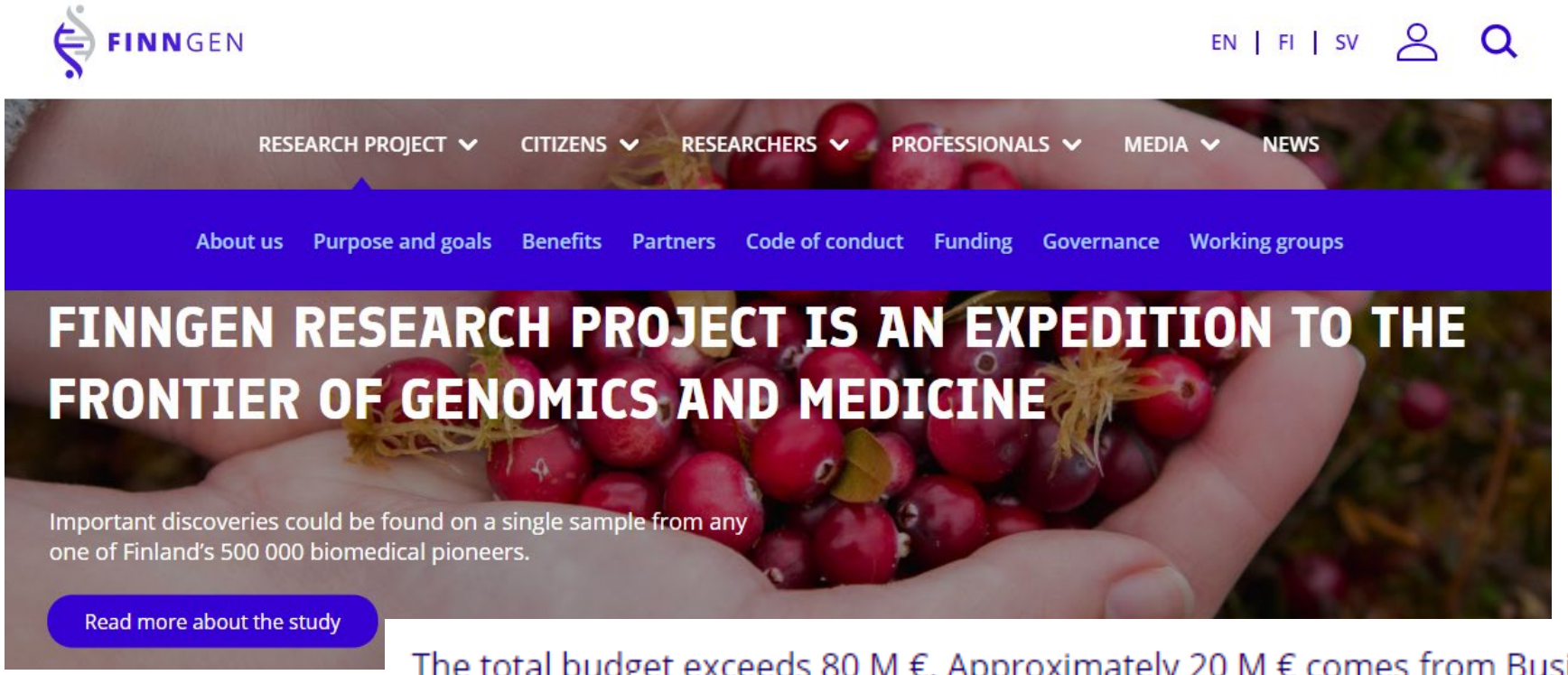
https://ec.europa.eu/digital-single-market/en/european-1-million-genomes-initiative


- **18 April 2018:** Declaration of cooperation
- **Signed by 24 Member States (19 January 2023)** and …**the UK and Norway**

FINNGEN

## FUNDING

FinnGen study is funded by Business Finland and the pharmaceutical industry partners. The funding allocated for the first three years (FinnGen1: 2017-2020) is approximately 40 M €. The whole budget exceeds 80 M€.




The total budget exceeds 80 M €. Approximately 20 M € comes from Business Finland and the rest from the international pharmaceutical industry partners: AbbVie, AstraZeneca, Biogen, Celgene/Bristol-Myers Scibb, Genentech (a member of the Roche Group), GSK, Janssen, Maze Therapeutics, MSD/Merck, Novartis, Pfizer and Sanofi.

1+ MILLION GENOMES BELGIUM

BELGIUM

BGB
BELGIAN GENOME BIOBANK



The 12 topics addressed by the Belgium 1+MG Mirror Group are listed below and the primary scope is indicated between brackets:

- Maturity model
- Ethical, Legal, and Societal Issues (ELSI)
- Clinical and phenotypic data
- Good sequencing practice / standards on data quality
- ICT
- Health economics
- Stakeholders
- Case : Rare Diseases
- Case : Cancer
- Case : Personalised prevention/population based sequencing
- Case : Covid

## Ethical, Legal, and Societal Issues (ELSI)

Ethical, Legal, and Societal Issues (ELSI) - Minimum recommendation on ELSI and data protection (policy-support, ethics-legal)
Participants:
**Romain Alderweireldt**, Fondation 101 Génomes, Brussels
**Pascal Borry**, The Catholic University of Leuven ( KU Leuven), Leuven
**Jean-Marc Van Gyseghem**, University of Namur / Research Centre Information Law and Society, Namur
**Wannes Van Hoof**, Sciensano, Brussels

## Case : Rare Diseases

Use case - Rare diseases (lab-technical, clinical, population-health, ethics-legal)*
Participants:
**Romain Alderweireldt**, Fondation 101 Génomes, Brussels
**Karen Colaert**, Vlaams agentschap Zorg en Gezondheid (ZG), Brussels
**Karin Dahan**, Institute of Pathology and Genetics (IPG), Charleroi
**Elfride De Baere**, Ghent University & Ghent University Hospital (UZ Gent), Ghent
**Charlotte De Vogelaere**, Sciensano, Brussels
**François Dufrasne**, Université de Mons (UMONS), Mons
**Bart Loeys**, Antwerp University Hospital, Antwerp
**Frank Kooy**, The University of Antwerp (UAntwerp), Antwerp
**Geert Mortier**, Antwerp University Hospital, Antwerp
**Emile Van Schaftingen**, Catholic University Louvain (UCLouvain), Leuven
**Miikka Vikkula**, Catholic University Louvain (UCLouvain) / de Duve Institute, Leuven

# Ehler-Danlos

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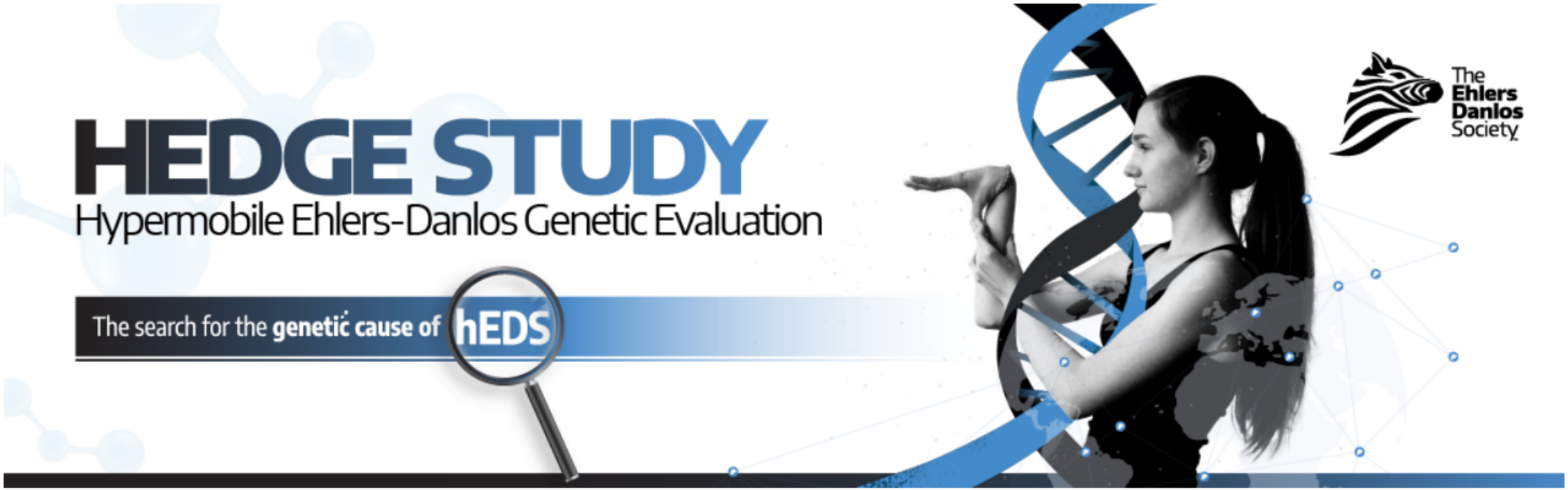
# HEDGE STUDY



The Ehlers-Danlos Society

Who We Are | EDS & HSD Info | Community Resour

# LARA BLOOM

**President and CEO**
The Ehlers-Danlos Society

Academic Affiliate Professor of Practice in Patient Engagement and Global Collaboration (Penn State College of Medicine)

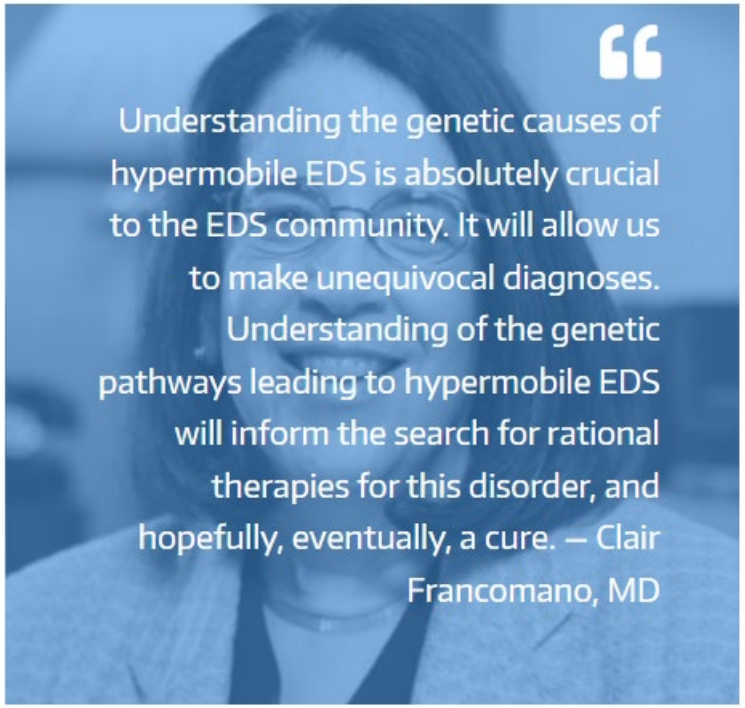
Lara Bloom is the Presiden
and invisible diseases, spec
disorders. Before joining th

Lara manages coordinated
HSD. She speaks at confere
field by offering her experi

Lara regularly works with u
and CEO of The Ehlers-Dar
Diseases International, Co-
the European Reference N
of the GenTAC Alliance Pati
Healthcare Products Regul

In 2016 Lara completed exp
Patients Academy EUPATI.

Lara played a key role in th
published author on the su




*Since the announcement of the extraordinary "Moonshot" donation in early 2018, which was then followed by a generous matching donation in early 2019, The Ehlers-Danlos Society brought together a highly experienced international group of physicians, geneticists, and technical volunteers to form the Hypermobile EDS Genetic Research Network which has now evolved to become the Hypermobility Biology Network, dedicated to finding the genetic cause, or causes of hEDS.*

Over 2019, 2020, and 2021, the HEDGE study will recruit, screen, and undertake genetic sequencing tests on 1000 individuals who have been diagnosed with hypermobile EDS by the most recent clinical criteria established in 2017.

# HEDGE STUDY

Hypermobile Ehlers-Danlos Genetic Evaluation

The search for the genetic cause of hEDS

## Biobank

The Genetic Alliance Precision for Medicine Biobank is responsible for storing all collected blood samples for the HEDGE study.

## Whole-Genome Sequencing

Sequencing of the DNA samples is scheduled to begin at the world-renowned Broad Institute of MIT and Harvard.

**Will my research data be kept confidential?**

Yes. The EDS Global Registry data is securely stored on LinaDNA and held in an environment that is compliant with rules related to privacy and security of information, including those of European General Data Protection Regulation (GDPR). To learn more about the LunaDNA platform and about the EDS Global Registry please refer to the frequently asked questions (FAQ) listed at the **bottom of the EDS Global registry page**.

luna

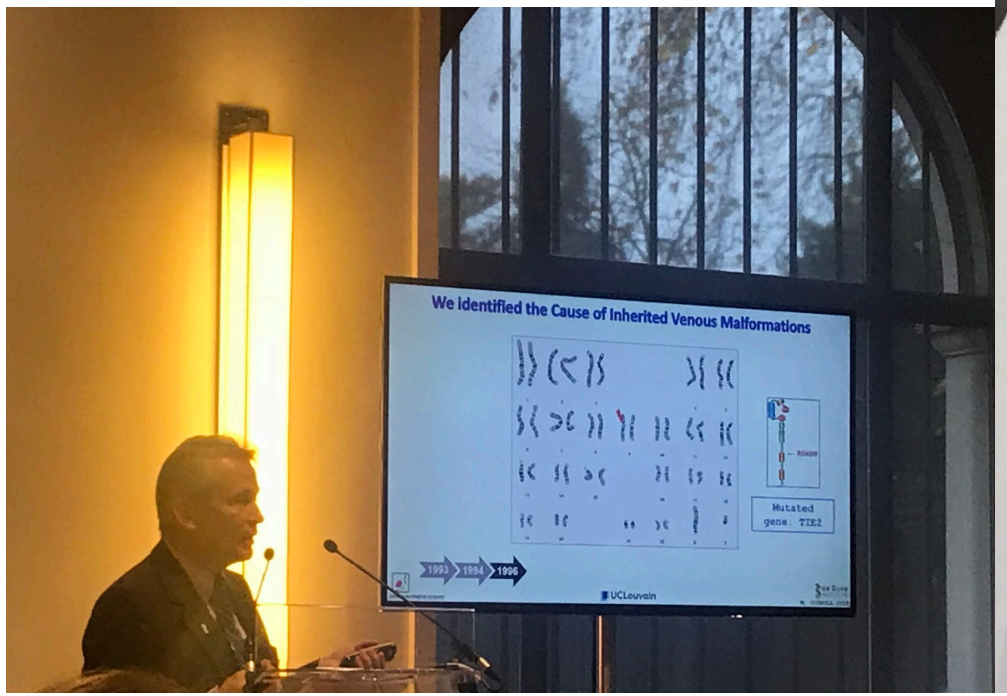
“

We dreamed of finding a way to give individuals and their communities the tools to take charge of their health and quest for treatments. Most technologies are people-centered in name only. We sought a partner who truly understood the importance of placing people at the center. With Luna, our dream has come true.”

Sharon Terry

GENETIC ALLIANCE

# VASCA





orphanet

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## Etiology

VMCMs are associated with amino acid substitutions (R849W and Y897S) in the tyrosine-protein kinase endothelial cell receptor (*TEK*/*TIE2*; 9p21). Approximately 90% of individuals who have a mutation in the *TEK* gene develop mucocutaneous venous malformations by 20 years of age; conversely, approximately 10% of individuals with a *TEK* mutation are clinically unaffected.

# Hereditary hemorrhagic telangiectasia

## Etiology

This genetic disorder is due to pathogenic variants primarily in *ENG* (9q34.11) or *ACVRL1* (12q13.13), encoding proteins involved in vascular development and angiogenic homeostasis of capillaries. Mutations in *SMAD4* (18q21.2) occur in rare cases (1-3%) and result in HHT associated with juvenile polyposis. In a small proportion of HHT families, the pathogenic gene variant has not yet been identified.

https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=236&Disease_Disease_Search_diseaseGroup=maladie-de-rendu-osler&Disease_Disease_Search_diseaseType=Pat&Maladie(s)/groupes%20de%20maladies=Telangiectasie-hemorragique-hereditaire&title=T%E9langiectasie%20h%E9morragique%20h%E9r%E9ditaire&search=Disease_Search_Simple

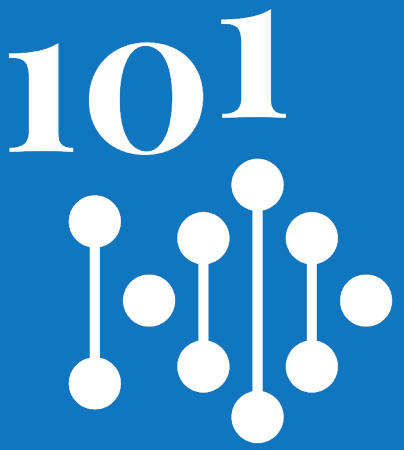
# Primary lymphedema

## Table 1 Genes implicated in isolated and syndromic lymphedema forms

From: Primary lymphedema French National Diagnosis and Care Protocol (PNDS; Protocole National de Diagnostic et de Soins)

| Syndrome | OMIM number | Associated clinical signs (non-exhaustive list) | Gene(s) implicated | Inheritance | Estimated prevalence (Orphanet 2018) |
|---|---|---|---|---|---|
| Milroy syndrome | #153100 | – | *FLT4/VEGFR3* | AD | 1/2500 to 1/10,000 |
| Milroy-like syndrome | #615907 | – | *VEGFC* | AD | < 1/100,000 |
| Meige syndrome | #613480 | – | *GJC2* | AD | < 1/100,000 |
| Turner syndrome (X-monosomy) | | Short stature<br>Ovarian insufficiency<br>Bone anomalies<br>Deafness<br>Cardiovascular malformations<br>Digestive malformations<br>Cardiac malformations | – | de novo | 1/2500 to 1/10,000 |
| Down syndrome (trisomy 21) | #190685 | Facial dysmorphy<br>Digestive malformations<br>Skeletal malformations<br>Cardiac malformations<br>Extremities anomalies<br>Hypotony | – | AD | 1/2500 to 1/10,000 |
| Noonan syndrome types 1 and 4 | #163950<br>#610733 | Arterial pulmonary stenosis<br>Facial dysmorphy<br>Pterygium colli (webbed neck)<br>Learning difficulties | *PTPN11*<br>*SOS1* | AD | 1/2500 to 1/10,000 |
| CM-AVM syndrome | #608354 | Capillary malformations<br>Arteriovenous malformations | *RASA1* | AD/mosaic | 1/10,000 to 1/100,000 |
| Lymphedema–distichiasis | #153400<br>#153300 | Distichiasis<br>Ungual dystrophy | *FOXC2* | AD | 1/10,000 to 1/100,000 |
| Emberger's syndrome | #614038 | Facial dysmorphy<br>Deafness<br>Pancytopenia<br>Myelodysplasia | *MET*<br>*HGF*<br>*GATA2* | AD | 1/100,000 to 1/1,000,000 |

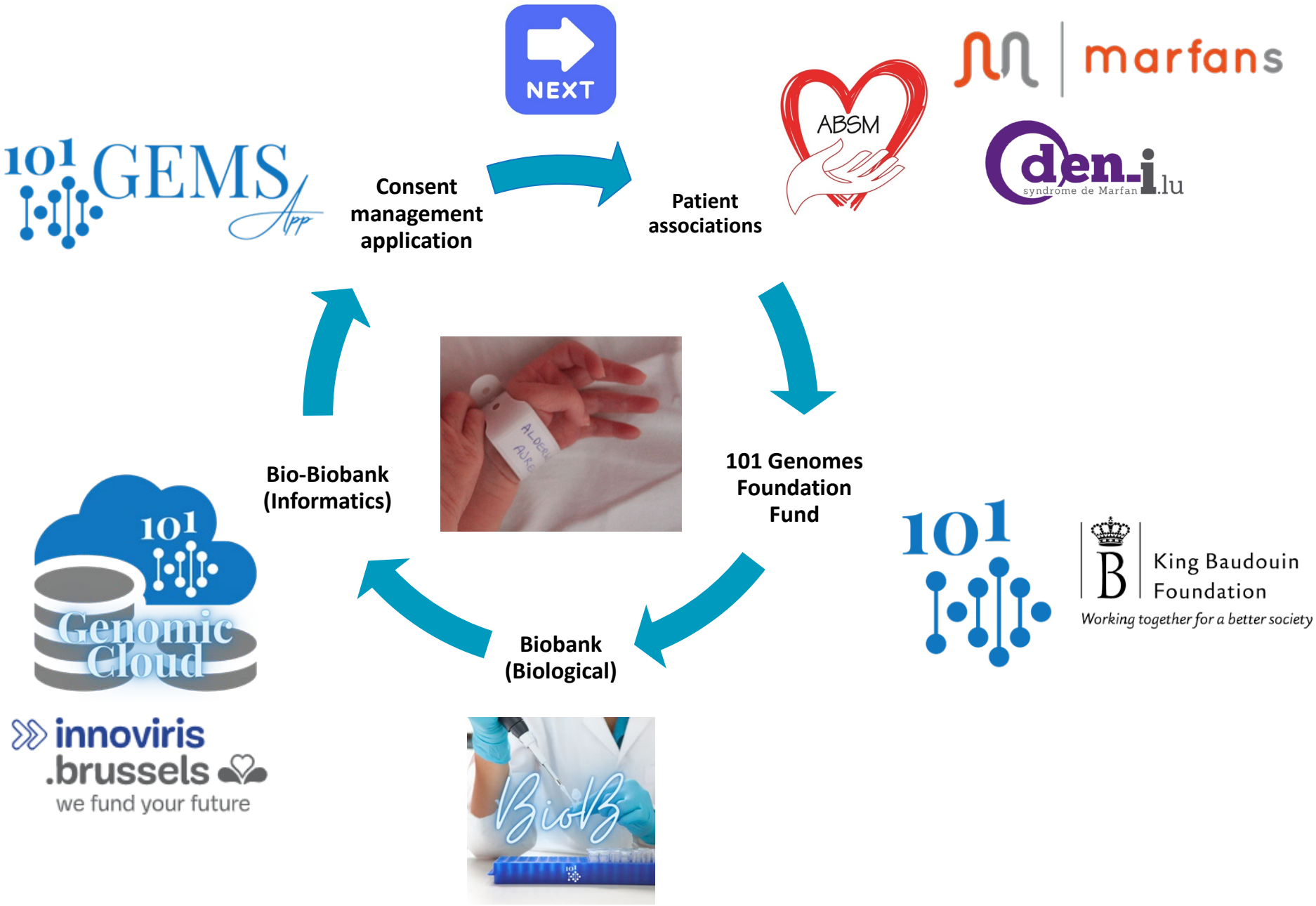
https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01652-w/tables/1




# Conclusion

# Sparkle

- Limited to 101 genomes, our initiative **is only a sparkle** in comparison with other state actions **but it can grow**.
- This sparkle is currently concentrated on Marfan syndrome **but it can be extended to other rare diseases**.
- This sparkle is a **patient driven initiative**.
- Our ambition is to provide the scientific community with **what they need to better understand rare diseases**.
- Our dream is that it could **contribute to the development of new drugs that could improve our children's lives**.
- **Join us!**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ABSM
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# 101 Genomes Foundation

Genomics for Rare Diseases

**Why are some children sick when they shouldn't be?** Why are some adults not sick when they should be?

Part of the answer to these questions **lies in our genes**.

In the context of **rare diseases**, this answer **could lead to therapies** for diseases that are currently **incurable**.

The **101 Genomes Foundation** supports **genomic and bioinformatics research** to find an answer to these questions and one day **better diagnose** and **treat** rare diseases.

**www.f101g.org**

*Research dedicated to rare diseases is advancing* ***the understanding of the human genome*** *and this knowledge is paving the way for the treatment of rare and much less rare diseases.*

***People with rare diseases have a lot to offer to all of us as a reward for what we have to do to help them.***

With the support of the **King Baudouin Foundation**, Ludivine and Romain Alderweireldt-Verboogen created the 101 Genomes Foundation to help children who, like their little boy, suffer from a rare disease.

They decided to make available to researchers a **Genomic Biobank *in the Cloud*** that contains the complete genomic data (WGS) of people with rare diseases and "control" people.

Since 2017, accompanied by renowned **scientists**, **patient associations**, generous **donors**, **lawyers** and **engineers**, they have been working to implement this solution.

Their **goal** is to advance research by creating a solution that will allow exploration of the genome to better understand rare childhood diseases and to better treat them.

**Why?** By examining a genetic database of healthy individuals who serve as controls for the research, Romain discovered that it contained many **variants on the FBN1 gene** that are considered in the scientific literature to be **pathogenic variants** that cause **the most severe forms** of Marfan syndrome.

The discovery of **apparently healthy** individuals with pathogenic variants suggests that they may be **genetically protected** from even the most severe forms of Marfan syndrome by the action of a so-called **protective gene able to counteract the failure of the FBN1 gene** that causes the disease.

The identification of possible protective genes in the genome would allow us **to envisage new therapeutic avenues that would replicate their protective effects**.

The action of the 101 Genomes Foundation is initially focused on a rare multi-system disease called **Marfan syndrome** with the will to **extend it to other rare diseases**.

By supporting our action, you are first supporting research dedicated to Marfan syndrome but you are also supporting **a broader approach that benefits many research groups** active in the field of rare diseases.

**101 Genomes Foundation**
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**www.f101g.org**

Support us by making a donation deductible in all European countries via the 101 Genomes Fund hosted by the King Baudouin Foundation:
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